

PCT

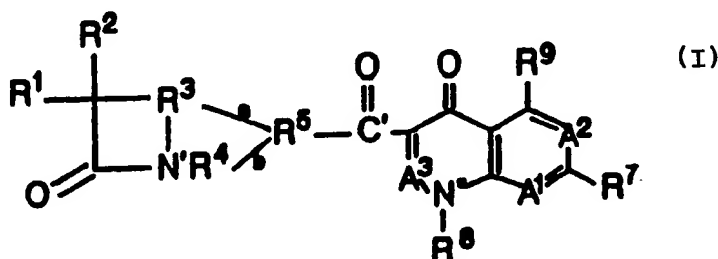
WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | |
|---|-----------|--|
| <p>(51) International Patent Classification n⁵ : C07D 499/00, A61K 31/425</p> | <p>A1</p> | <p>(11) International Publication Number: WO 90/04594 (43) International Publication Date: 3 May 1990 (03.05.90)</p> |
| <p>(21) International Application Number: PCT/US89/04803 (22) International Filing Date: 24 October 1989 (24.10.89) (30) Priority data: 261,798 24 October 1988 (24.10.88) US 418,033 12 October 1989 (12.10.89) US (71) Applicant: NORWICH EATON PHARMACEUTICALS, INC. [US/US]; 17 Eaton Avenue, Norwich, NY 13815 (US). (72) Inventors: DEMUTH, Thomas, Prosser, Jr. ; RD4, Box 161, Norwich, NY 13815 (US). WHITE, Ronald, Eugene ; Star Route Box 214, South Plymouth, NY 13844 (US). (74) Agents: WITTE, Monte, Dale et al.; The Procter & Gamble Company, Winton Hill Technical Center, 6060 Center Hill Road, Cincinnati, OH 45224 (US).</p> | | <p>(81) Designated State: JP. Published <i>With international search report.</i></p> |

(54) Title: NOVEL ANTIMICROBIAL QUINOLONYL LACTAM ESTERS



(57) Abstract

Antimicrobial quinolonyl lactam esters comprising a lactam-containing moiety linked, by an ester group, to the 3-carboxy group of a quinolone moiety. These compounds are of formula (I), wherein (1) R³, R⁴, and R⁵, together with bonds "a" and "b", form certain lactam-containing moieties similar to those known in the art to have antimicrobial activity; and (2) A, R⁶, R⁷, and R⁸ form any of a variety of quinolone or naphthyridine structures similar to those known in the art to have antimicrobial activity.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | |
|----|------------------------------|----|--|----|--------------------------|
| AT | Austria | ES | Spain | MG | Madagascar |
| AU | Australia | FI | Finland | ML | Mali |
| BB | Barbados | FR | France | MR | Mauritania |
| BE | Belgium | GA | Gabon | MW | Malawi |
| BF | Burkina Faso | GB | United Kingdom | NL | Netherlands |
| BG | Bulgaria | HU | Hungary | NO | Norway |
| BJ | Benin | IT | Italy | RO | Romania |
| BR | Brazil | JP | Japan | SD | Sudan |
| CA | Canada | KP | Democratic People's Republic of Korea | SE | Sweden |
| CF | Central African Republic | KR | Republic of Korea | SN | Senegal |
| CG | Congo | LI | Liechtenstein | SU | Soviet Union |
| CH | Switzerland | LK | Sri Lanka | TD | Chad |
| CM | Cameroon | LU | Luxembourg | TG | Togo |
| DE | Germany, Federal Republic of | MC | Monaco | US | United States of America |
| DK | Denmark | | | | |

NOVEL ANTIMICROBIAL QUINOLONYL LACTAM ESTERS

5

BACKGROUND OF THE INVENTION

This invention relates to novel antimicrobial compounds and compositions. The compounds of this invention contain a quinolone moiety and a lactam-containing moiety, in a new chemical entity.

10 The chemical and medical literature describes a myriad of compounds that are said to be antimicrobial, i.e., capable of destroying or suppressing the growth or reproduction of microorganisms, such as bacteria. In particular, antibacterials include a large variety of naturally-occurring (antibiotic),
15 synthetic, or semi-synthetic compounds. They may be classified (for example) as the aminoglycosides, ansamacrolides, beta-lactams (including penicillins and cephalosporins), lincosaminides, macrolides, nitrofurans, nucleosides, oligosaccharides, peptides and polypeptides, phenazines, polyenes, polyethers,
20 quinolones, tetracyclines, and sulfonamides. Such antibacterials and other antimicrobials are described in Antibiotics, Chemotherapeutics, and Antibacterial Agents for Disease Control (M. Grayson, editor, 1982), and E. Gale et al., The Molecular Basis of Antibiotic Action 2d edition (1981), both incorporated
25 by reference herein.

The mechanism of action of these antibacterials vary. However, each can be generally classified as functioning in one or more of four ways: by inhibiting cell wall synthesis or
30 repair; by altering cell wall permeability; by inhibiting protein synthesis; or by inhibiting synthesis of nucleic acids. For

-2-

example, beta-lactam antibacterials act through inhibiting the essential penicillin binding proteins (PBPs) in bacteria, which are responsible for cell wall synthesis. On the other hand, quinolones act by inhibiting synthesis of bacterial DNA, thus preventing the bacteria from replicating.

Not surprisingly, the pharmacological characteristics of antibacterials and other antimicrobials, and their suitability for any given clinical use, also vary considerably. For example, the classes of antimicrobials (and members within a class) may vary in their relative efficacy against different types of microorganisms, and their susceptibility to development of microbial resistance. These antimicrobials may also differ in their pharmacological characteristics, such as their bioavailability, and biodistribution. Accordingly, selection of an appropriate antibacterial (or other antimicrobial) in any given clinical situation can be a complicated analysis of many factors, including the type of organism involved, the desired method of administration, and the location of the infection to be treated.

The development of microbial resistance is one factor in the selection of an appropriate antimicrobial (particularly antibacterials), which is of increasing concern in medical science. This "resistance" can be defined as existence of organisms, within a population of a given microbial species, that are less susceptible to the action of a given antimicrobial agent. Such resistant strains may subvert the mechanism of action of a particular antimicrobial, or chemically degrade the antimicrobial before it can act. For example, bacterial resistance to beta-lactam antibacterials has arisen through development of bacterial strains that produce beta-lactamase enzymes, which degrade the antibacterial.

In part as a result of the intense use of antibacterials over extended periods of time, many highly resistant strains of bacteria have evolved. This is of particular concern in environments such as hospitals and nursing homes, which are characterized by relatively high rates of infection and intense

-3-

use of antibacterials. See, e.g., W. Sanders, Jr. et al., "Inductible Beta-lactamases: Clinical and Epidemiologic Implications for Use of Newer Cephalosporins", 10 Reviews of Infectious Diseases 830 (1988). Indeed, the development of resistant bacterial strains has led to a concern that pathogenic bacteria may be produced that are essentially resistant to even the newest developed antibacterial agents.

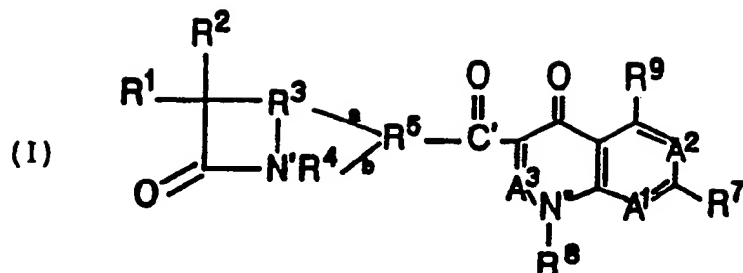
The literature describes many attempts to enhance the efficacy of antimicrobials, and to overcome the development of microbial resistance. Many such attempts involve the combination of antimicrobials. For example, Thabaut et al., 16 Presse Med. 2167 (1987) describes combinations of pefloxacin (a quinolone) with the beta-lactams cefotaxime and cefsulodin. Lenoc et al., 36 Path. Biol. 762 (1988), describes combined use of cepheims with aminoglycosides, and with quinolones. Japanese Patent Publication 60/06,617, published January 14, 1985, also describes compositions containing beta-lactams and quinolones. O'Callaghan et al., 10 Antimicrobial Agents and Chemotherapy 245 (1976), describes a mercapto pyridine-substituted cephem, which is said to liberate an active antimicrobial agent when the cephalosporin is hydrolyzed by beta-lactamase. Mobashery et al., 108 J. American Chemical Society 1684 (1986), presents a theory of employing bacterial beta-lactamase in situ to release an antibacterially-active leaving group from the 10-position of a cephem.

However, many such attempts to produce improved antimicrobials yield equivocal results. Indeed, few antimicrobials are produced that are truly clinically-acceptable in terms of their spectrum of antimicrobial activity, avoidance of microbial resistance, and pharmacology.

SUMMARY OF THE INVENTION

The present invention provides compounds of the formula:

-4-



wherein

(A) R¹ is hydrogen, halogen, alkyl, alkenyl, heteroalkyl, a carbocyclic ring, a heterocyclic ring, R^{10a}-O-, R^{10a}CH=N-, (R¹⁰)(R¹¹)N-, R¹²-C(=CHR¹⁵)-C(=O)NH-, R¹²-C(=NO-R¹⁴)-C(=O)NH-, or R¹³-(CH₂)_m-C(=O)NH-; where

(1) m is an integer from 0 to 9;

(2) R¹⁰ and R¹¹ are, independently, R^{10a} where R^{10a} is hydrogen, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring substituent; or R¹⁰ and R¹¹ together comprise a heterocyclic ring including the nitrogen to which they are bonded;

(3) R¹² is hydrogen, alkyl, alkenyl, heteroalkyl, heteroalkenyl, a carbocyclic ring, or a heterocyclic ring;

(4) R¹³ is R¹², -Z¹, or -CH(Z²)(R¹²);

(5) R¹⁴ is R¹², arylalkyl, heteroarylalkyl, -C(R¹⁷)(R¹⁸)COOH, -C(=O)O-R¹², or -C(=O)NH-R¹², where R¹⁷ and R¹⁸ are, independently, R¹² or together comprise a carbocyclic ring or a heterocyclic ring including the carbon atom to which R¹⁷ and R¹⁸ are bonded;

(6) R¹⁵ is R¹⁴, halogen, -Z¹, or -CH(Z²)(R¹²);

(7) Z¹ is -C(=O)OR¹⁶, -C(=O)R¹⁶, -N(R¹⁹)R¹⁶, -S(O)_pR²⁴, or -OR²⁴; and Z² is Z¹ or -OH, -SH, or -SO₃H;

(a) p is an integer from 0 to 2;

-5-

- 5 (b) R¹⁹ is hydrogen; alkyl; alkenyl; heteroalkyl; heteroalkenyl; a carbocyclic ring; a heterocyclic ring; -SO₃H; -C(=O)R²⁰; or, when R¹³ is -CH(Z²)(R¹²) and Z² is -N(R¹⁹)R¹⁶, R¹⁹ may comprise a moiety bonded to R¹⁶ to form a heterocyclic ring; and
- 10 (c) R²⁰ is R¹², NH(R¹²), N(R¹²)(R²¹), O(R²¹), or S(R²¹); where R²¹ is alkyl, alkenyl, a carbocyclic ring, a heterocyclic ring, or when R²⁰ is N(R¹²)(R²¹) R²¹ may be a moiety bonded to R¹² to form a heterocyclic ring; and
- 15 (8) R¹⁶ is R²⁴ or hydrogen; where R²⁴ is alkyl; alkenyl; arylalkyl; heteroalkyl; heteroalkenyl; heteroarylalkyl; a carbocyclic ring; a heterocyclic ring; or, when Z¹ is N(R¹⁹)R¹⁶ and R¹⁶ is R²⁴, R¹⁶ and R¹⁹ may together comprise a heterocyclic ring including the nitrogen atom to which R¹⁹ is bonded;
- 20 (B) R² is hydrogen, halogen, alkoxy, or R²²C(=O)NH-, where R²² is hydrogen or alkyl;
- (C) bond "a" is a single bond or is nil; and bond "b" is a single bond, a double bond, or is nil; except bond "a" and bond "b" are not both nil;
- 25 (D) R³ is -C(R^{10a})-, or -CH₂-R²³-; where R²³ is -C(R^{10a}), -O-, or -N-, and R²³ is directly bonded to N' in Formula (I) to form a 5-membered ring;
- except, if bond "a" is nil, then R³ is
- (1) -C(R^{10a})(Z³)-, where
- 30 (i) Z³ is -R¹⁶, -OR²⁵, -S(O)_rR²⁵, where r is an integer from 0 to 2, -OC(=O)R²⁵, or -N(R²⁵)R²⁶;
- (ii) R²⁵ and R²⁶ are, independently, alkyl, alkenyl, carbocyclic ring or heterocyclic ring substituents; or R²⁵ and R²⁶ together comprise a heterocyclic ring including the nitrogen atom to which R²⁵ and R²⁶ are bonded; or
- 35

-6-

- (2) $-\text{CH}_2-\text{R}^{27}-$; where R^{27} is $-\text{C}(\text{R}^{10a})(\text{R}^{16})$, $-\text{O}-$, or $-\text{NR}^{10a}$, and R^{27} is directly bonded to N' in Formula (I) to form a 5-membered ring;
- (E) (1) if bond "b" is a single bond, R^4 is $-\text{CH}(\text{R}^{28})-$; or, if bond "a" is nil; $-\text{C}(\text{O})\text{NHSO}_2-$; or $-\text{C}^*(\text{R}^{28})-$; if R^5 contains an R^{32} moiety; where R^{28} is hydrogen or COOH , and C^* is linked to R^{32} to form a 3-membered ring;
- (2) if bond "b" is a double bond, R^4 is $-\text{C}(\text{R}^{28})=$; or
- (3) if bond "b" is nil, R^4 is hydrogen, $-\text{SO}_3\text{H}$, $-\text{PO}(\text{OR}^{29})\text{OH}$, $-\text{C}(\text{O})\text{NHSO}_2\text{N}(\text{R}^{29})(\text{R}^{30})$, $-\text{OSO}_3\text{H}$, $-\text{CH}(\text{R}^{30})\text{COOH}$, or $-\text{OCH}(\text{R}^{29})\text{COOH}$; where R^{29} is hydrogen, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring; and R^{30} is hydrogen, alkyl, alkenyl, or $-\text{NHR}^{10a}$; or, if R^4 is $-\text{C}(\text{O})\text{NHSO}_2\text{N}(\text{R}^{29})(\text{R}^{30})$, R^{29} and R^{30} may together comprise a heterocyclic ring including the nitrogen to which R^{29} and R^{30} are bonded; and
- (F) (1) if bond "a" or bond "b" is nil, then R^5 is Y;
- (2) if bond "a" and "b" are single bonds, R^5 is $-\text{X}^2-\text{C}''=\text{C}(\text{R}^{10a})-\text{R}^{31}-\text{Y}-$, or $-\text{X}^2-\text{C}''(\text{R}^{32})-\text{R}^{31}-\text{Y}-$; or
- (3) if bond "a" is a single bond and bond "b" is a double bond, R^5 is $-\text{C}(\text{R}^{10a})(\text{R}^{33})-\text{X}^2-\text{C}''-\text{R}^{31}-\text{Y}-$; $-\text{X}^1-\text{C}(\text{R}^{10a})(\text{R}^{33})-\text{C}''-\text{R}^{31}-\text{Y}-$; or $-\text{X}^2-\text{C}''-\text{R}^{31}-\text{Y}-$; where
- (a) X^1 is O or $\text{C}(\text{R}^{33})$, where R^{33} is hydrogen, alkyl or alkoxy;
- (b) X^2 is O; $\text{S}(\text{O})_s$, where s is an integer from 0 to 2; or $\text{C}(\text{R}^{33})$;
- (c) R^{31} is nil, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring;
- (d) R^{32} is hydrogen; alkyl; alkenyl; $-\text{COOH}$; or, if R^4 is $-\text{C}^*(\text{R}^{28})$, R^{32} may be linked to C^* to form a 3-membered carbocyclic ring;
- (e) Y is O or $\text{Z}^4-\text{R}^{34}-\text{O}$, where
- (1) Z^4 is $-\text{O}-$; $-\text{S}(\text{O})_t-$, where t is an integer of 0 to 2; or $-\text{NR}^{10a}-$; and

-7-

(2) R³⁴ is alkyl, alkenyl, heteroalkyl, heteroalkenyl, a carbocyclic ring, or a heterocyclic ring; and

(3) Y is directly bonded to C'

5 (f) C'' is bonded to R⁴ to form a 5- or 6-membered ring;

(G) (1) A¹ is N or C(R⁴⁰); where R⁴⁰ is hydrogen, hydroxy, alkoxy, nitro, cyano, halogen, alkyl, or N(R¹⁰)(R¹¹), and

10 (2) A² is N or C(R⁶); where R⁶ is hydrogen or halogen;

(3) A³ is N or C(R⁴¹); where R⁴¹ is hydrogen;

(4) R⁸ is hydrogen, alkyl, a carbocyclic ring, a heterocyclic ring, alkoxy, hydroxy, alkenyl, arylalkyl, or N(R¹⁰)(R¹¹);

15 (5) R⁷ is hydrogen, halogen, alkyl, a carbocyclic ring, or a heterocyclic ring; and

(7) R⁹ is hydrogen, halogen, nitro, or N(R¹⁰)(R¹¹);

(H) except that

20 (1) when A¹ is C(R⁴⁰), R⁸ and R⁴⁰ may together comprise a heterocyclic ring including N'' and A¹;

(2) when A² is C(R⁶), R⁶ and R⁷ may together comprise -O-(CH₂)_n-O-, where n is an integer from 1 to 4; and

25 (3) when A³ is C(R⁴¹), R⁸ and R⁴¹ may together comprise a heterocyclic ring including N'' and the adjacent carbon to which R⁴¹ is bonded;

and pharmaceutically-acceptable salts and biohydrolyzable esters thereof, and hydrates thereof.

30 It has been found that the compounds of this invention, and compositions containing these compounds, are effective antimicrobial agents against a broad range of pathogenic microorganisms. These compounds provide advantages versus antimicrobial agents among those known in the art, including (for example) the spectrum of antimicrobial activity, potency, the avoidance of microbial resistance, reduced toxicity, and improved

35 pharmacology.

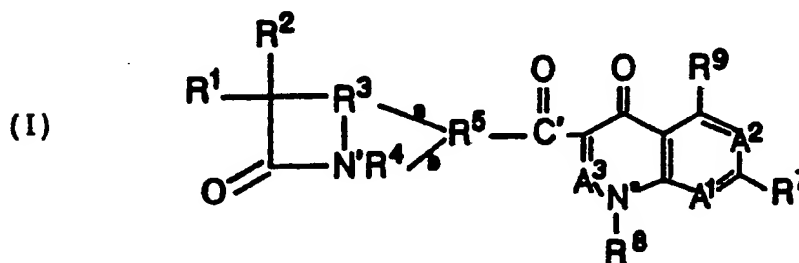
-8-

DESCRIPTION OF THE INVENTION

The present invention encompasses certain novel quinolonyl lactam esters, methods for their manufacture, dosage forms, and methods of administering the quinolonyl lactam esters to a human or other animal subject. Specific compounds and compositions to be used in the invention must, accordingly, be pharmaceutically acceptable. As used herein, such a "pharmaceutically-acceptable" component is one that is suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio.

Quinolonyl Lactam Esters

The compounds of this invention, herein referred to as "quinolonyl lactam esters", encompass any of a variety of lactam-containing moieties linked, by an ester linkage, to the 3-carboxy group of a quinolone moiety. These compounds include those of the formula:



wherein

- (A) R¹ is hydrogen, halogen, alkyl, alkenyl, heteroalkyl, a carbocyclic ring, a heterocyclic ring, R^{10a}-O-, R^{10a}CH=N-, (R¹⁰)(R¹¹)N-, R¹²-C(=CHR¹⁵)-C(=O)NH-, or (preferably) R¹²-C(=NO-R¹⁴)-C(=O)NH-, or R¹³-(CH₂)_m-C(=O)NH-; where
- (1) m is an integer from 0 to 9 (preferably 0 to 3);
 - (2) R¹⁰ and R¹¹ are, independently, R^{10a} where R^{10a} is hydrogen, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring substituent; or R¹⁰ and R¹¹ together

-9-

comprise a heterocyclic ring including the nitrogen to which they are bonded;

- (3) R¹² is hydrogen, alkyl, alkenyl, heteroalkyl, heteroalkenyl, a carbocyclic ring, or a heterocyclic ring (preferably alkyl, a carbocyclic ring, or a heterocyclic ring);
- (4) R¹³ is R¹², -Z¹, or -CH(Z²)(R¹²);
- (5) R¹⁴ is R¹², arylalkyl, heteroarylalkyl, -C(R¹⁷)(R¹⁸)COOH, -C(=O)O-R¹², or -C(=O)NH-R¹², where R¹⁷ and R¹⁸ are, independently, R¹² or together comprise a carbocyclic ring or a heterocyclic ring including the carbon atom to which R¹⁷ and R¹⁸ are bonded (preferably R¹² or -C(R¹⁷)(R¹⁸)COOH;
- (6) R¹⁵ is R¹⁴, halogen, -Z¹, or -CH(Z²)(R¹²) (preferably R¹⁹ or halogen);
- (7) Z¹ is -C(=O)OR¹⁶, -C(=O)R¹⁶, -N(R¹⁹)R¹⁶, -S(O)_pR²⁴, or -OR²⁴; and Z² is Z¹ or -OH, -SH, or -SO₃H;
- (a) p is an integer from 0 to 2 (preferably 0);
- (b) R¹⁹ is hydrogen; alkyl; alkenyl; heteroalkyl; heteroalkenyl; a carbocyclic ring; a heterocyclic ring; -SO₃H; -C(=O)R²⁰; or, when R¹³ is -CH(Z²)(R¹²) and Z² is -N(R¹⁹)R¹⁶, R¹⁹ may comprise a moiety bonded to R¹⁶ to form a heterocyclic ring; and
- (c) R²⁰ is R¹², NH(R¹²), N(R¹²)(R²¹), O(R²¹), or S(R²¹) (preferably R¹², NH(R¹²), N(R¹²)(R²¹)); where R²¹ is alkyl, alkenyl, a carbocyclic ring, a heterocyclic ring, or (preferably) when R²⁰ is N(R¹²)(R²¹) R²¹ may be a moiety bonded to R¹² to form a heterocyclic ring; and
- (8) R¹⁶ is R²⁴ or hydrogen; where R²⁴ is alkyl; alkenyl; arylalkyl; heteroalkyl; heteroalkenyl; heteroarylalkyl; a carbocyclic ring; a heterocyclic ring; or, when Z¹ is N(R¹⁹)R¹⁶ and R¹⁶ is R²⁴, R¹⁶ and R¹⁹ may together comprise a heterocyclic ring including the nitrogen

-10-

atom to which R¹⁹ is bonded (preferably hydrogen, alkyl, a carbocyclic ring or a heterocyclic ring);

(B) R² is hydrogen, halogen, alkoxy, or R²²C(=O)NH- (preferably hydrogen or alkoxy), where R²² is hydrogen or alkyl (preferably hydrogen);

(C) bond "a" is a single bond or is nil; and bond "b" is a single bond, a double bond, or is nil; except bond "a" and bond "b" are not both nil;

(D) R³ is -C(R^{10a})-, or -CH₂-R²³- (preferably -C(R^{10a})-); where R²³ is -C(R^{10a}), -O-, or -N-, and R²³ is directly bonded to N' in Formula (I) to form a 5-membered ring;

except, if bond "a" is nil, then R³ is

(1) (preferably) -C(R^{10a})(Z³)-, where

(i) Z³ is -R¹⁶, -OR²⁵, -S(O)_rR²⁵-, where r is an integer from 0 to 2 (preferably 0), -OC(=O)R²⁵, or -N(R²⁵)R²⁶;

(ii) R²⁵ and R²⁶ are, independently, alkyl, alkenyl, carbocyclic ring or heterocyclic ring substituents; or R²⁵ and R²⁶ together comprise a heterocyclic ring including the nitrogen atom to which R²⁵ and R²⁶ are bonded; or

(2) -CH₂-R²⁷-; where R²⁷ is -C(R^{10a})(R²⁴), -O-, or -NR¹⁰, and R²⁷ is directly bonded to N" in Formula (II) to form a 5-membered ring;

(E) (1) if bond "b" is a single bond, R⁴ is (preferably) -CH(R²⁸)-; or, if bond "a" is nil; -C(O)NHSO₂-; or -C*(R²⁸)-; if R⁵ contains a R- moiety; where R²⁸ is hydrogen or (preferably) COOH, and C* is linked to R- to form a 3-membered ring;

(2) if bond "b" is a double bond, R⁴ is -C(R²⁸)=; or

(3) if bond "b" is nil, R⁴ is hydrogen, -SO₃H, -PO(OR²⁹)OH, -C(O)NHSO₂N(R²⁹)(R³⁰), -OSO₃H, -CH(R³⁰)COOH, or -OCH(R²⁹)COOH (preferably -SO₃H or -C(O)NHSO₂N(R²⁹)(R³⁰)); where R²⁹ is hydrogen, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring; and R³⁰ is hydrogen, alkyl, alkenyl, or -NHR^{10a}; or

-11-

(preferably), if R^4 is $-C(O)NHSO_2N(R^{29})(R^{30})$, R^{29} and R^{30} may together comprise a heterocyclic ring including the nitrogen to which R^{29} and R^{30} are bonded; and

- (F) (1) if bond "a" or bond "b" is nil, then R^5 is Y;
- 5 (2) if bond "a" and "b" are single bonds, R^5 is $-X^2-C''=C(R^{10a})-R^{31}-Y-$, or $-X^2-C''(R^{32})-R^{31}-Y-$; or
- (3) (preferably) if bond "a" is a single bond and bond "b" is a double bond, R^5 is $-C(R^{10a})(R^{33})-X^2-C''-R^{31}-Y-$; or (preferably) $-X^1-C(R^{10a})(R^{33})-C''-R^{31}-Y-$; or
- 10 $-X^2-C''-R^{31}-Y-$, where
- (a) X^1 is O or $C(R^{33})$, where R^{33} is hydrogen, alkyl or alkoxy;
- (b) X^2 is O; $S(O)_s$, where s is an integer from 0 to 2 (preferably 0); or $C(R^{33})$;
- 15 (c) R^{31} is nil, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring;
- (d) R^{32} is hydrogen; alkyl; alkenyl; $-COOH$; or, if R^4 is $-C^*(R^{28})$, R^{32} may be linked to C^* to form a 3-membered carbocyclic ring;
- 20 (e) Y is O or $Z^4-R^{34}-O$, where
- (1) Z^4 is $-O-$; $-S(O)_t-$, where t is an integer of 0 to 2 (preferably 0); or $-NR^{10a}-$; and
- (2) R^{34} is alkyl, alkenyl, heteroalkyl, heteroalkenyl, a carbocyclic ring, or a heterocyclic ring (preferably alkyl or alkenyl); and
- 25 (3) Y is directly bonded to C'
- (f) C'' is bonded to R^4 to form a 5- or 6-membered ring;
- 30 (G) (1) A^1 is N or $C(R^{40})$; where R^{40} is hydrogen, hydroxy, alkoxy, nitro, cyano, halogen, alkyl, or $N(R^{10})(R^{11})$ (preferably hydrogen or halogen), and
- (2) A^2 is N or (preferably) $C(R^6)$; where R^6 is hydrogen or halogen;
- 35 (3) A^3 is N or (preferably) $C(R^{41})$; where R^{41} is hydrogen;

-12-

- (4) R^8 is hydrogen, alkyl, a carbocyclic ring, a heterocyclic ring, alkoxy, hydroxy, alkenyl, arylalkyl, or $N(R^{10})(R^{11})$ (preferably hydrogen or a carbocyclic ring);
- 5 (5) R^7 is hydrogen, halogen, alkyl, a carbocyclic ring, or a heterocyclic ring (preferably a heterocyclic ring); and
- (7) R^9 is hydrogen, halogen, nitro, or $N(R^{10})(R^{11})$;
- (H) except that
- 10 (1) when A^1 is $C(R^{40})$, R^8 and R^{40} may together comprise a heterocyclic ring including N' and A^1 ;
- (2) when A^2 is $C(R^6)$, R^6 and R^7 may together comprise $-O-(CH_2)_n-O-$, where n is an integer from 1 to 4; and
- 15 (3) when A^3 is $C(R^{41})$, R^8 and R^{41} may together comprise a heterocyclic ring including N'' and the adjacent carbon to which R^{41} is bonded;

and pharmaceutically-acceptable salts and biohydrolyzable esters thereof, and hydrates thereof.

20 Definitions and Usage of Terms:

The following is a list of definitions for terms used herein.

25 "Heteroatom" is a nitrogen, sulfur or oxygen atom. Groups containing one or more heteroatoms may contain different heteroatoms.

"Alkyl" is an unsubstituted or substituted saturated hydrocarbon chain radical having from 1 to 8 carbon atoms, preferably from 1 to 4 carbon atoms. Preferred alkyl groups
30 include (for example) methyl, ethyl, propyl, isopropyl, and butyl.

"Heteroalkyl" is an unsubstituted or substituted saturated chain radical having from 3 to 8 members comprising carbon atoms and one or two heteroatoms.

35

-13-

"Alkenyl" is an unsubstituted or substituted hydrocarbon chain radical having from 2 to 8 carbon atoms, preferably from 2 to 4 carbon atoms, and having at least one olefinic double bond.

5 "Carbocyclic ring" is an unsubstituted or substituted, saturated, unsaturated or aromatic, hydrocarbon ring radical. Carbocyclic rings are monocyclic or are fused, bridged or spiro polycyclic ring systems. Monocyclic rings contain from 3 to 9 atoms, preferably 3 to 6 atoms. Polycyclic rings contain from 7 to 17 atoms, preferably from 7 to 13 atoms.

10 "Cycloalkyl" is a saturated carbocyclic ring radical. Preferred cycloalkyl groups include (for example) cyclopropyl, cyclobutyl and cyclohexyl.

"Heterocyclic ring" is an unsubstituted or substituted, saturated, unsaturated or aromatic ring radical comprised of 15 carbon atoms and one or more heteroatoms in the ring. Heterocyclic rings are monocyclic or are fused, bridged or spiro polycyclic ring systems. Monocyclic rings contain from 3 to 9 atoms, preferably 3 to 6 atoms. Polycyclic rings contain from 7 to 17 atoms, preferably from 7 to 13 atoms.

20 "Aryl" is an aromatic carbocyclic ring radical. Preferred aryl groups include (for example) phenyl, tolyl, xylyl, cumenyl and naphthyl.

"Heteroaryl" is an aromatic heterocyclic ring radical. Preferred heteroaryl groups include (for example) thienyl, furyl, 25 pyrrolyl, pyridinyl, pyrazinyl, thiazolyl, pyrimidinyl, quinolonyl, and tetrazolyl.

"Alkoxy" is an oxygen radical having a hydrocarbon chain substituent, where the hydrocarbon chain is an alkyl or alkenyl (i.e., -O-alkyl or -O-alkenyl). Preferred alkoxy groups include 30 (for example) methoxy, ethoxy, propoxy and allyloxy.

"Alkylamino" is an amino radical having one or two alkyl substituents (i.e., -N-alkyl).

"Arylalkyl" is an alkyl radical substituted with an aryl group. Preferred arylalkyl groups include benzyl and 35 phenylethyl.

-14-

"Arylamino" is an amine radical substituted with an aryl group (i.e., -NH-aryl).

"Aryloxy" is an oxygen radical having a aryl substituent (i.e., -O-aryl).

5 "Acyl" or "carbonyl" is a radical formed by removal of the hydroxy from an carboxylic acid (i.e., R-C(=O)-). Preferred alkylacyl groups include (for example) acetyl, formyl, and propionyl.

10 "Acyloxy" is an oxygen radical having an acyl substituent (i.e., -O-acyl); for example, -O-C(=O)-alkyl.

"Acylamino" is an amino radical having an acyl substituent (i.e., -N-acyl); for example, -NH-C(=O)-alkyl.

"Halo", "halogen", or "halide" is a chloro, bromo, fluoro or iodo atom radical. Chloro and fluoro are preferred halides.

15 Also, as referred to herein, a "lower" hydrocarbon moiety (e.g., "lower" alkyl) is a hydrocarbon chain comprised of from 1 to 6, preferably from 1 to 4, carbon atoms.

20 A "pharmaceutically-acceptable salt" is a cationic salt formed at any acidic (e.g., carboxyl) group, or an anionic salt formed at any basic (e.g., amino) group. Many such salts are known in the art, as described in World Patent Publication 87/05297, Johnston et al., published September 11, 1987 (incorporated by reference herein). Preferred cationic salts include the alkali metal salts (such as sodium and potassium),
25 and alkaline earth metal salts (such as magnesium and calcium). Preferred anionic salts include the halides (such as chloride salts).

30 A "biohydrolyzable ester" is an ester of a quinolonyl lactam ester that does not essentially interfere with the antimicrobial activity of the compounds, or that are readily metabolized by a human or lower animal subject to yield an antimicrobially-active quinolonyl lactam ester. Such esters include those that do not interfere with the biological activity of quinolone antimicrobials or beta-lactam antimicrobials (cephems, for
35 example). Many such esters are known in the art, as described in World Patent Publication 87/05297, Johnston et al., published

-15-

September 11, 1987, (incorporated by reference herein). Such esters include lower alkyl esters, lower acyloxy-alkyl esters (such as acetoxymethyl, acetoxyethyl, aminocarbonyloxymethyl, pivaloyloxymethyl and pivaloyloxyethyl esters), lactonyl esters (such as phthalidyl and thiophthalidyl esters), lower alkoxy-acyloxyalkyl esters (such as methoxycarbonyloxymethyl, ethoxycarbonyloxyethyl and isopropoxycarbonyloxyethyl esters), alkoxyalkyl esters, choline esters, and alkyl acylamino alkyl esters (such as acetamidomethyl esters).

As defined above and as used herein, substituent groups may themselves be substituted. Such substitution may be with one or more substituents. Such substituents include those listed in C. Hansch and A. Leo, Substituent Constants for Correlation Analysis in Chemistry and Biology (1979), incorporated by reference herein. Preferred substituents include (for example) alkyl, alkenyl, alkoxy, hydroxy, oxo, nitro, amino, aminoalkyl (e.g., aminomethyl, etc.), cyano, halo, carboxy, alkoxyaceyl (e.g., carboethoxy, etc.), thiol, aryl, cycloalkyl, heteroaryl, heterocycloalkyl (e.g., piperidinyl, morpholinyl, pyrrolidinyl, etc.), imino, thioxo, hydroxyalkyl, aryloxy, arylalkyl, and combinations thereof.

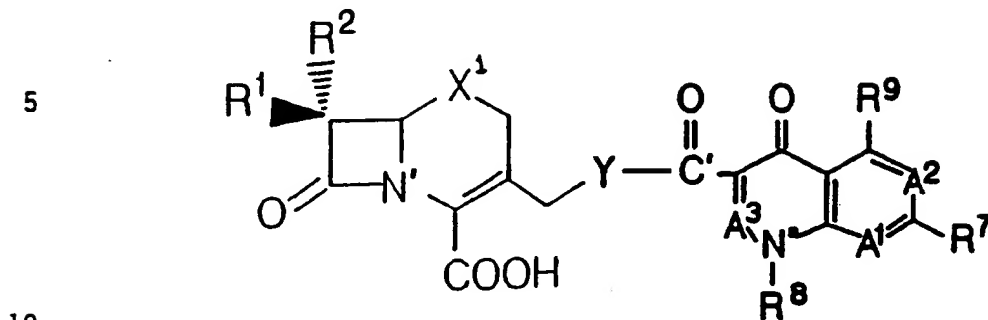
Also, as used in defining the structure of the compounds of this invention, a particular radical may be defined for use as a substituent in multiple locations. For example, the R^{10a} substituent is defined as a potential substituent of R¹, but is also incorporated into the definition of other substituents (such as R³, R⁸, and R⁹). As used herein, such a radical is independently selected each time it is used (e.g., R^{10a} need not be alkyl in all occurrences in defining a given compound of this invention).

Lactam-containing moieties:

Groups R³, R⁴, and R⁵, together with bonds "a" and "b", form any of a variety of lactam-containing moieties known in the art to have antimicrobial activity. Such moieties wherein either bond "a" or bond "b" are nil (i.e., do not exist) are monocyclic; if both bonds exist, the structures are bicyclic.

-16-

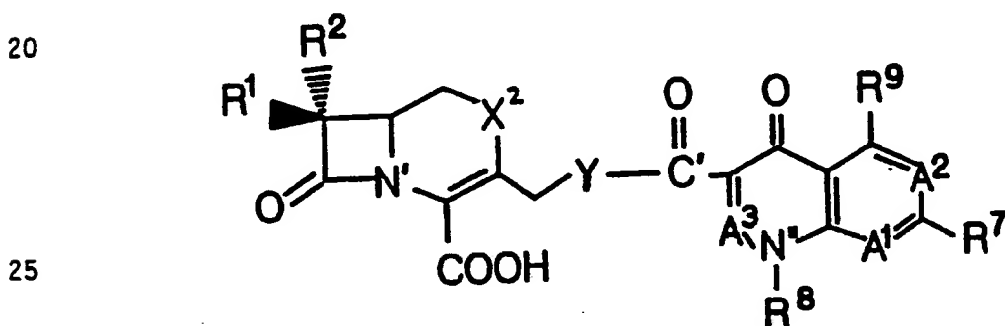
Preferred lactam moieties include the oxacephems and carbacephems of the representative formula:



wherein bond "a" is a single bond; bond "b" is a double bond; R³ is -C(R^{10a})-, where R^{10a} is hydrogen; R⁴ is -CH(R²⁸), where R²⁸ is COOH; and R⁵ is -X¹-C(R^{10a})(R³³)-C''-R³¹-Y-, where R^{10a} and R³³ are hydrogen, R³¹ is methylene, and X¹ is O (for oxacephems) or C(R³³) (for carbacephems).

15

Other preferred lactam moieties include the isocephems and iso-oxacephems of the representative formula:



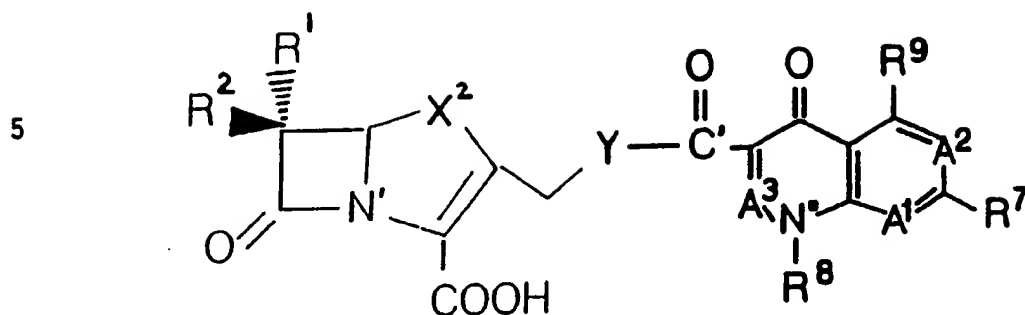
wherein bond "a" is a single bond; bond "b" is a double bond; R³ is -C(R^{10a} where R^{10a} is hydrogen; R⁴ is -C(R²⁸), where R²⁸ is COOH; and R⁵ is -C(R^{10a})(R³³)-X²-C''-R³¹-Y- where R^{10a} and R³³ are each hydrogen, R³¹ is methylene, and X² is S (for isocephems) or O (for iso-oxacephems).

30

Other preferred lactam-containing moieties include the penems, carbapenems and clavams, of the representative formula:

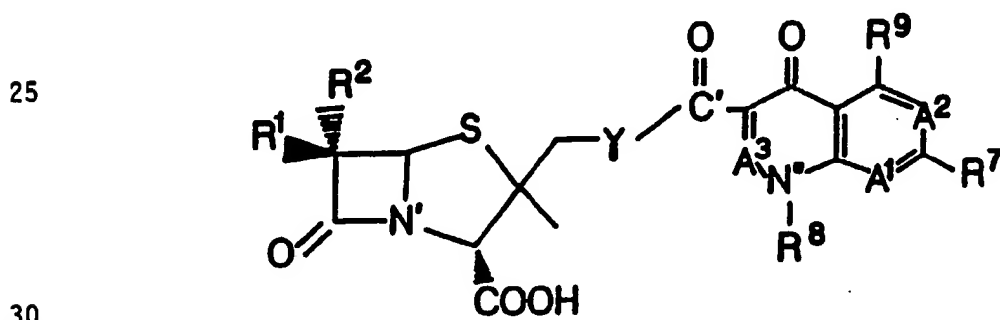
35

-17-



wherein bond "a" is a single bond; bond "b" is a double bond; R³ is -C(R^{10a}), where R^{10a} is hydrogen; R⁴ is -C(R²⁸)=, where R²⁸ is COOH; and R⁵ is -X²-C''-R³¹-Y-, where R³¹ is methylene, and X² is S (for penems), C(R³³) (for carbapenems), or O (for clavams). Such lactam moieties are described in the following articles, all incorporated by reference herein: R. Wise, "In Vitro and Pharmacokinetic Properties of the Carbapenems", 30 Antimicrobial Agents and Chemotherapy 343 (1986); and S. McCombie et al., "Synthesis and In Vitro Activity of the Penem Antibiotics", 8 Medicinal Research Reviews 393 (1988).

Other preferred lactam-containing moieties of this invention include the penicillins of the representative formula:

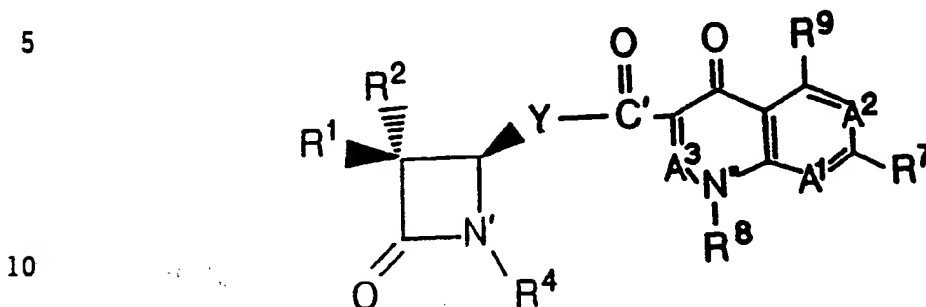


wherein bond "a" is a single bond, bond "b" is a single bond; R³ is -C(R^{10a})-, where R^{10a} is hydrogen; R⁴ is -CH(R²⁸)- where R²⁸ is COOH; and R⁵ is -X²-C''-(R³²)-R³¹-Y- where R³² is methyl, R³¹ is methylene, and X² is S.

35

-18-

Other preferred lactam-containing moieties include the monocyclic beta-lactams, of the representative formula:



wherein bond "a" is a single bond; bond "b" is nil; R³ is -C(R^{10a})-, where R^{10a} is hydrogen; R⁵ is Y; and R⁴ is -SO₃H (for a monobactam), -PO(OR³⁴)OH (for a monophospham);

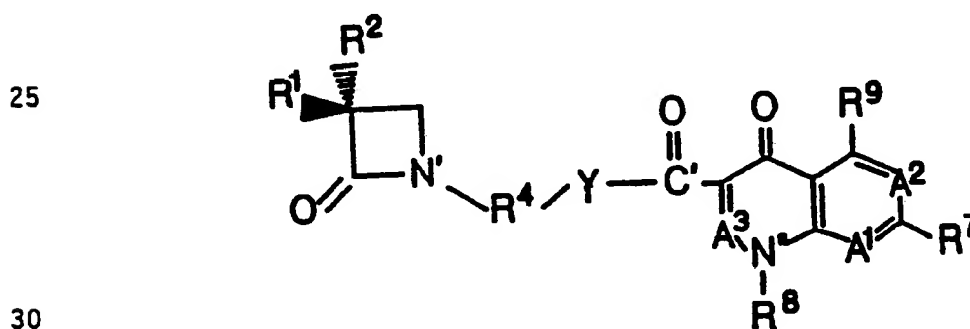
15

-C(O)NHSO₂N(R³⁴)(R³⁵) (for a monocarbam), -OSO₃H (for a monosulfactam), -CH(R³⁵)COOH (for nocardicins), or -OCH(R³⁴)COOH. Such lactam moieties are described in C. Cimarusti et al., "Monocyclic 8-lactam Antibiotics", 4 Medicinal Research Reviews 1

20

(1984), incorporated by reference herein.

Other preferred lactam moieties include the monocyclic beta-lactams of the representative formula:

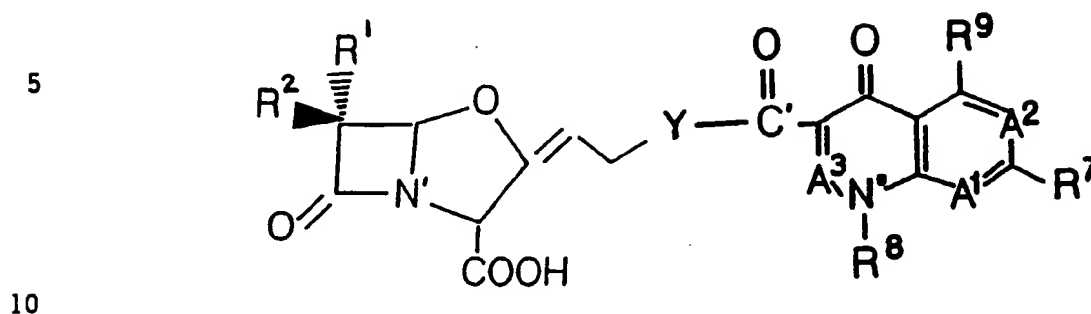


wherein bond "a" is nil, bond "b" is a single bond; R³ is -C(R^{10a})(R²⁹)- where both R^{10a} and R²⁹ are hydrogen; and R⁵ is Y.

35

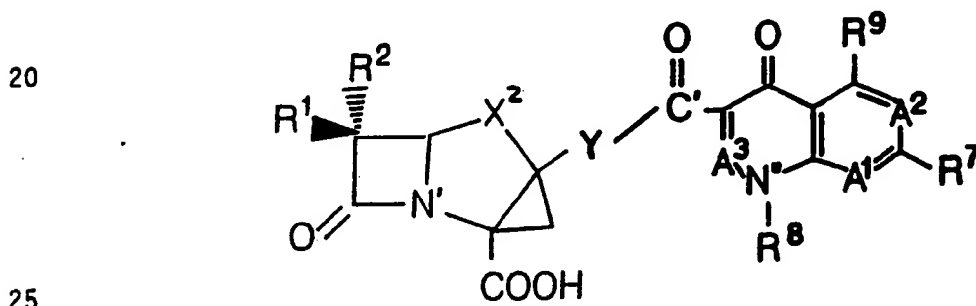
-19-

Other preferred lactam moieties include the clavams of the representative formula:



wherein bond "a" is a single bond; bond "b" is a single bond; R³ is -C(R^{10a})-, where R^{10a} is hydrogen; R⁴ is -CH(R²⁸)-, where R²⁸ is COOH; and R⁵ is X²-C''-C-(R^{10a})-R³¹-Y-, where R^{10a} is hydrogen and R³¹ is methylene, and X² is O.

Other preferred lactam moieties include the 2,3-methylenopenams and -carbapenams of the representative formula:

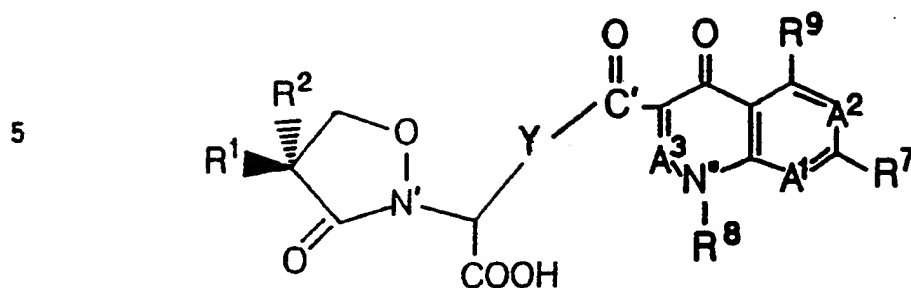


wherein bond "a" is a single bond; bond "b" is a single bond; R³ is -C(R^{10a})-, where R^{10a} is hydrogen; R⁴ is -C*(R²⁸), where R²⁸ is COOH; and R⁵ is X²-C''(R³²)-R³¹-Y-, where R³¹ is nil, R³² is linked to C* to form a 3-membered carbocyclic ring, and X² is C(R³³) or sulfur.

Lactam moieties of this invention also include the lactivicin analogs of the representative formula:

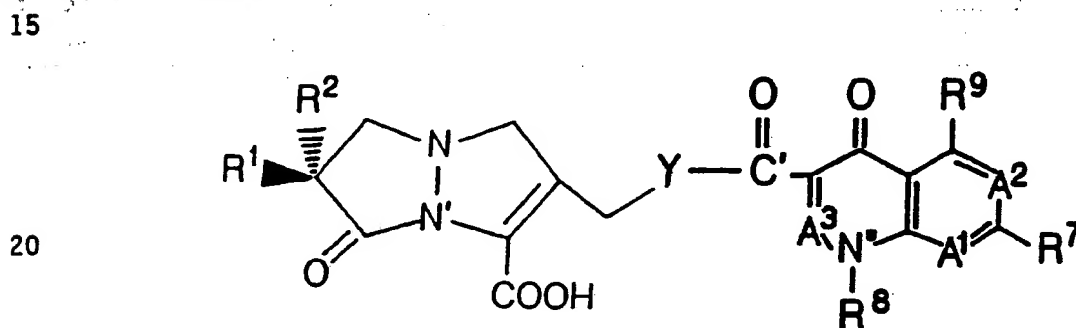
35

-20-



10 wherein bond "a" is nil; bond "b" is a single bond; R³ is -CH₂-R³², where R³² is O; R⁴ is -CH(R²⁸)-, where R²⁸ is COOH; and R⁵ is Y.

Other lactam moieties include the pyrazolidinones of the representative formula:



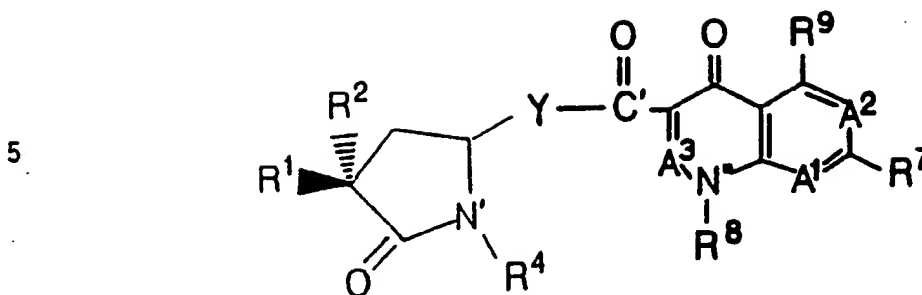
25 wherein bond "a" is a single bond; bond "b" is a double bond; R³ is -CH₂-R²⁸-, where R²⁸ is -N-; R⁴ is -C(R²⁸)-, where R²⁸ is COOH; and R⁵ is X²-C''-R³¹-Y-, where R³¹ is methylene, and X² is C(R³³).

Other lactam moieties include the gamma-lactams of the representative formula:

30

35

-21-



10 wherein bond "a" is a single bond; bond "b" is nil; R³ is -CH₂-R²⁸-, where R²⁸ is -C(R^{10a}) and R^{10a} is hydrogen; R⁴ is -SO₃H, -PO(OR³⁴)OH, -C(O)NHSO₂N(R³⁴)(R³⁵), -OSO₃H, -CH(R³⁵)COOH, or -OCH(R³⁴)COOH; and R⁵ is Y.

15 Preferred lactam-containing moieties include cephems, isocephems, iso-oxacephems, oxacephems, carbacephems, penicillins, penems, carbapenems, and monocyclic beta-lactams. Particularly preferred are cephems, penems, carbapenems and monocyclic beta-lactams.

20 R¹ is any radical that may be substituted at the active stereoisomeric position of the carbon adjacent to the lactam carbonyl of an antimicrobially-active lactam. (As used herein, the term "antimicrobially-active lactam" refers to a lactam-containing compound, without a quinolonyl substituent moiety, which has antimicrobial activity.) This "active" position is beta (i.e., 7-beta) for cephems, oxacephems and carbacephems (for example). The active position is alpha for penems, carbapenems, clavams and clavams.

25 Appropriate R¹ groups will be apparent to one of ordinary skill in the art. Many such R¹ groups are known in the art, as described in the following documents (all of which are incorporated by reference herein): Cephalosporins and Penicillins: Chemistry and Biology (E. Flynn, editor, 1972); Chemistry and Biology of b-Lactam Antibiotics (R. Morin et al., editors, 1987); "The Cephalosporin Antibiotics: Seminar-in-Print", 34 Drugs (Supp. 2) 1 (J. Williams, editor, 1987); New Beta-Lactam Antibiotics: A Review from Chemistry of

30

35

-22-

Clinical Efficacy of the New Cephalosporins (H. Neu, editor, 1982); M. Sassiver et al., in Structure Activity Relationships among the Semi-synthetic Antibiotics (D. Perlman, editor, 1977). W. Durckheimer et al., "Recent Developments in the Field of Beta-Lactam Antibiotics", 24 Angew. Chem. Int. Ed. Engl. 180 (1985); G. Rolinson, "Beta-Lactam Antibiotics", 17 J. Antimicrobial Chemotherapy 5 (1986); European Patent Publication 187,456, Jung, published July 16, 1986; and World Patent Publication 87/05297, Johnston et al., published September 11, 1987.

For penems, carbapenems, clavams and clavams, R^1 is preferably lower alkyl, or hydroxy-substituted lower alkyl. Particularly preferred R^1 groups include hydrogen, hydroxymethyl, ethyl, [1(R)-hydroxyethyl], [1(R)-[(hydroxysulfonyl)oxyethyl]], and [1-methyl-1-hydroxyethyl].

Except for penems, carbapenems, clavams and clavams, preferred R^1 groups are amides, such as: acetylamino, preferably substituted with aryl, heteroaryl, aryloxy, heteroarylthio and lower alkylthio substituents; arylglycylamino, preferably N-substituted with heteroarylcarbonyl and cycloheteroalkylcarbonyl substituents; arylcarbonylamino; heteroarylcarbonylamino; and lower alkoxyiminoacetylamino, preferably substituted with aryl and heteroaryl substituents. Particularly preferred R^1 groups include amides of the general formula $R^{13}-(CH_2)_m-C(=O)NH-$ and R^{13} is R^{12} . Examples of such preferred R^1 groups include:

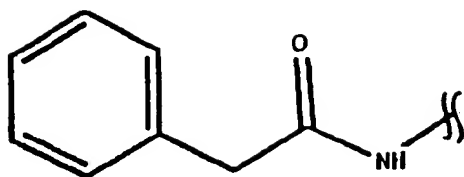
[(2-amino-5-halo-4-thiazolyl)acetyl]amino;
[(4-aminopyridin-2-yl)acetyl]amino;
[[[(3,5-dichloro-4-oxo-1(4H)-pyridinyl)acetyl]amino];
[[[2-(aminomethyl)phenyl]acetyl]amino];
[(1H-tetrazol-1-yl)acetyl]amino];
[(cyanoacetyl)amino];
[(2-thienylacetyl)amino];
[[[(2-amino-4-thiazoyl)acetyl]amino]; and
sydnone, 3-[-2-amino]-2-oxoethyl.

The following are other such preferred R^1 groups.

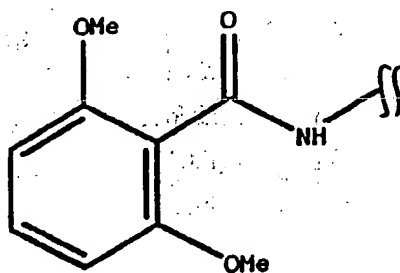
-23-

HCONH-

5

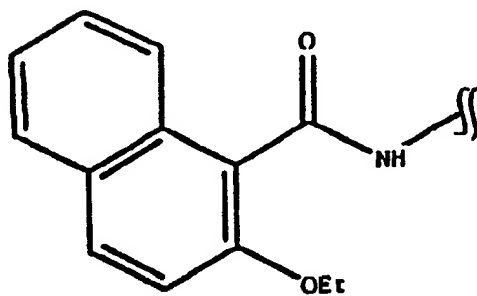


10



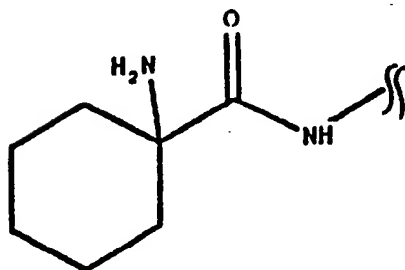
15

20



25

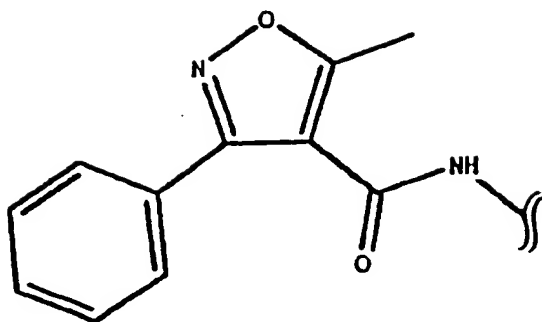
30



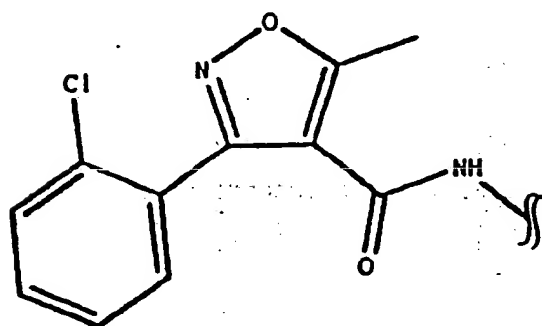
35

-24-

5

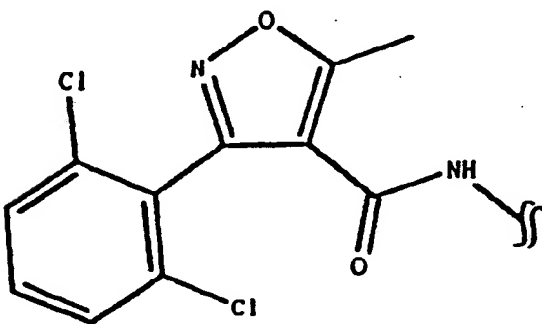


10



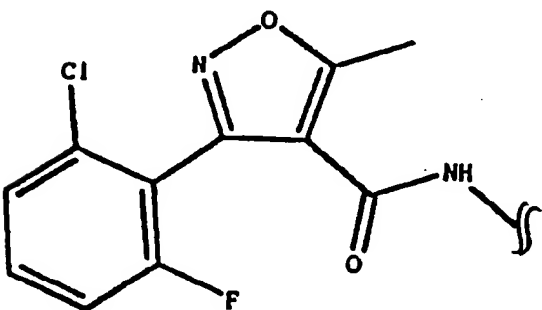
15

20



25

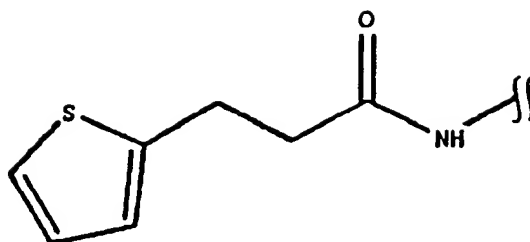
30



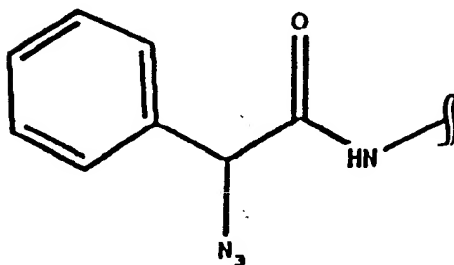
35

-25-

5

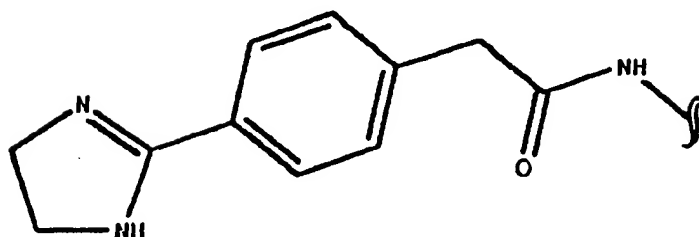


10



15

20



When R^1 is $R^{13}-(CH_2)_m-C(=O)NH-$, and R^{13} is $-Z^1$, preferred R^1 groups include the following:

25

[sulfamoylphenylacetyl]amino;

[[[4-pyridinylthio]acetyl]amino];

[[[(cyanomethyl)thio]acetyl]amino];

(S)-[[[(2-amino-2-carboxyethyl)thio]acetyl]amino];

[[[(trifluoromethyl)thio]acetyl]amino]; and

30

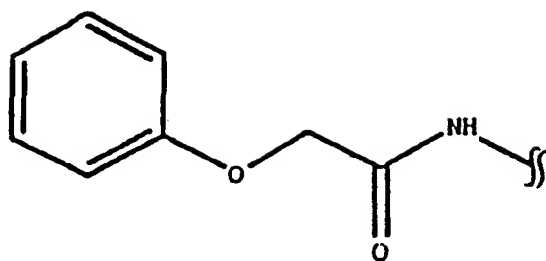
(E)-[[[(2-aminocarbonyl-2-fluoroethenyl)thio]acetyl]amino].

The following are other such preferred R^1 groups.

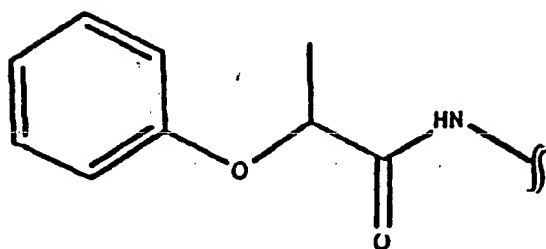
35

-26-

5

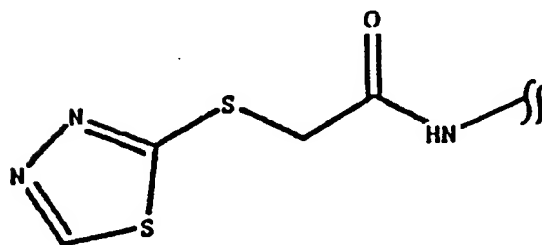


10

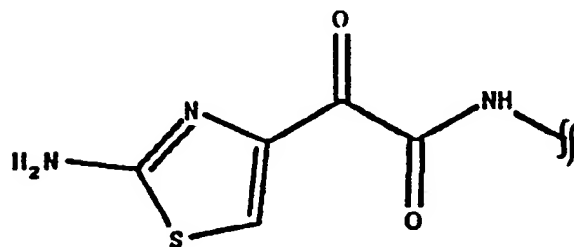


15

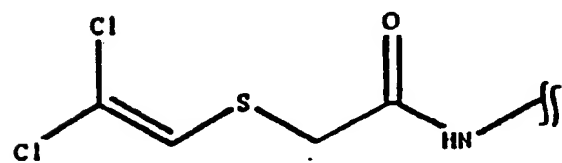
20



25



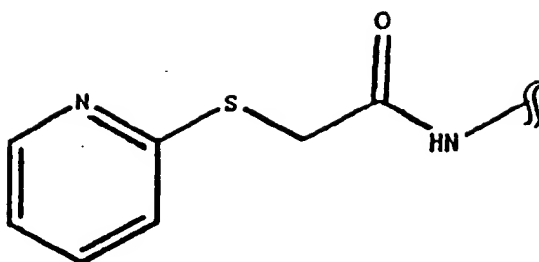
30



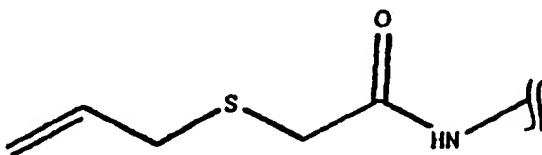
35

-27-

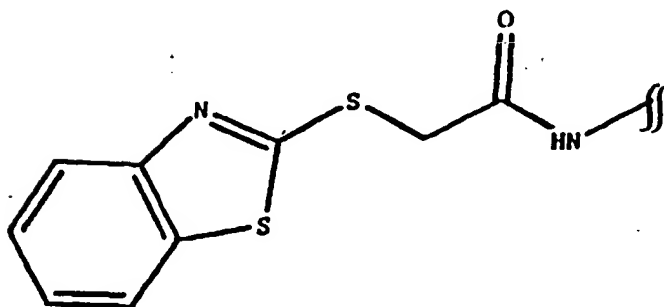
5



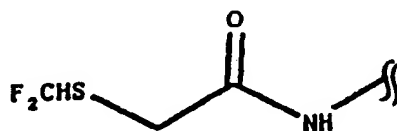
10



15



20



25



30

When R^1 is $R^{13}-(CH_2)_m-C(=O)NH-$, and R^{13} is $-CH(Z^2)(R^{12})$, preferred R^1 groups include the following:

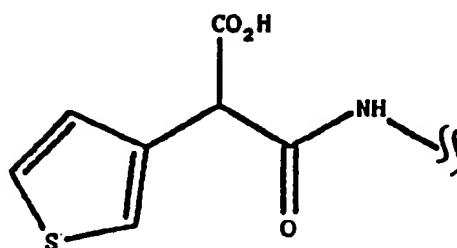
- [carboxyphenylacetyl]amino;
- [(phenoxyacetyl)phenylacetyl]amino;
- [4-methyl-2,3-dioxo-1-piperazinecarbonyl-D-phenylglycyl]-
- amino;

-28-

- [[3-(2-furylmethyleneamino)-2-oxo-1-imidazolidinyl]-
 carbonyl]amino]phenyl]acetyl]amino;
 (R)-[(aminophenylacetyl)amino];
 (R)-[[amino(4-hydroxyphenyl)acetyl]amino];
 5 (R)-[(amino-1,4-cyclohexadien-1-yl)acetyl]amino];
 [(hydroxyphenylacetyl)amino];
 (R)-[[[(4-ethyl-2,3-dioxo-1-piperazinyl)carbonyl]amino]-
 (4-hydroxyphenyl)acetyl]amino];
 (R)-[[[(5-carboxy-1H-imidazol-4-yl)carbonyl]amino]phenyl-
 10 acetyl]amino];
 (R)-[[[(4-hydroxy-6-methyl-3-pyridinyl)carbonyl]amino](4-
 hydroxyphenyl)acetyl]amino];
 (R)-[(phenylsulfoacetyl)amino];
 (2R,3S)-[[2-[[[(4-ethyl-2,3-dioxo-1-piperazinyl)carbonyl]-
 15 amino]-3-hydroxy-1-oxobutyl]amino];
 [[carboxy(4-hydroxyphenyl)acetyl]amino];
 (R)-[[amino[3-[(ethylsulfonyl)amino]phenyl]acetyl]amino];
 (R)-[[amino(benzo[b]thien-3-yl)acetyl]amino];
 (R)-[[amino(2-naphthyl)acetyl]amino];
 20 (R)-[[amino(2-amino-4-thiazolyl)acetyl]amino];
 [[[(6,7-dihydroxy-4-oxo-4H-1-benzopyran-3-yl)carbonyl]-
 amino](4-hydroxyphenyl)acetyl]amino];
 (R,R)-[[2-[4-[2-amino-2-carboxyethyloxycarbonyl]aminophen-
 yl]-2-hydroxyacetyl]amino]; and
 25 (S)-[[[(5-hydroxy-4-oxo-1(4H)-pyridin-2-yl)carbonyl]amino(2-
 amino-4-thiazolyl)acetyl]amino].

The following are other such preferred R¹ groups.

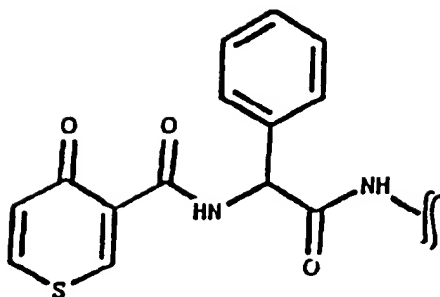
30



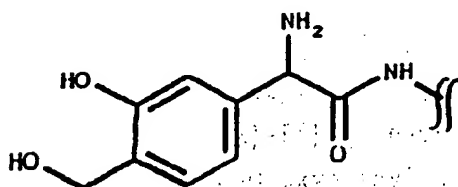
35

-29-

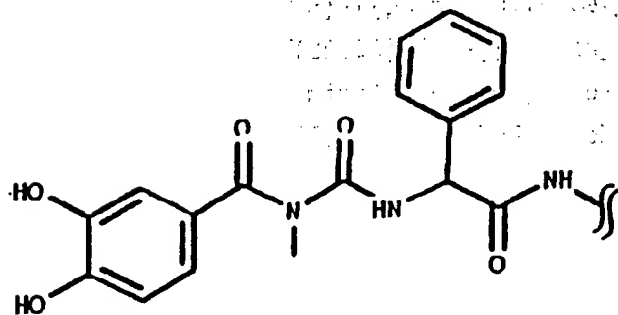
5



10

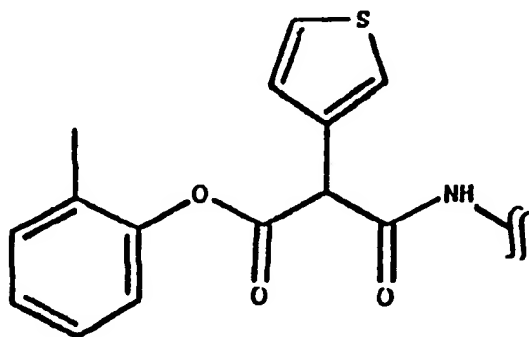


15



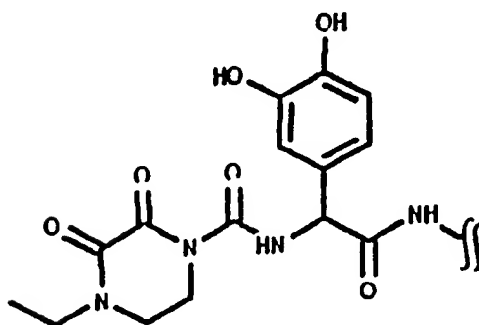
20

25



30

35



-30-

5

10

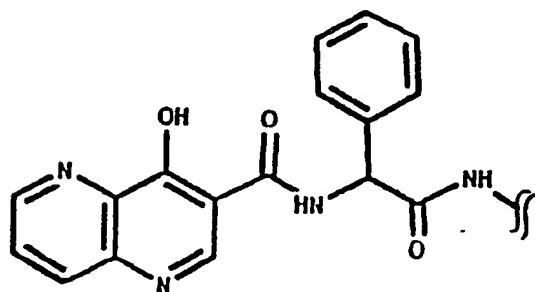
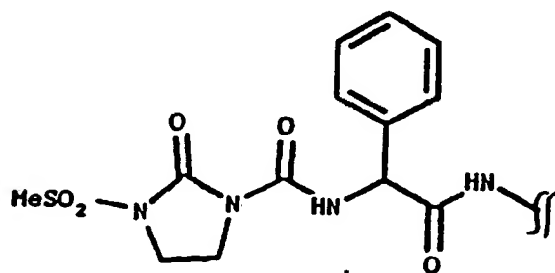
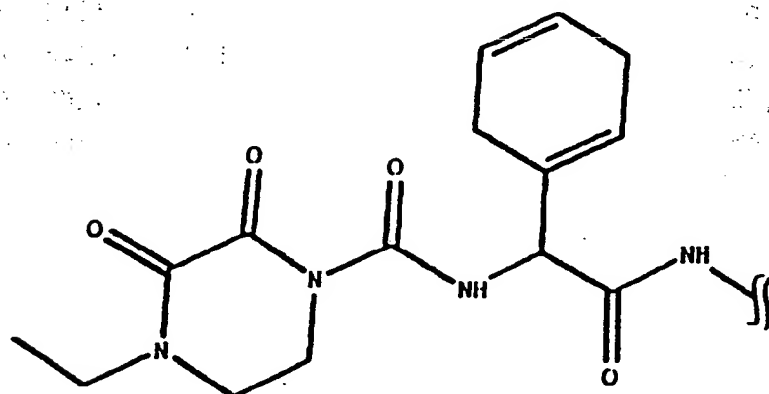
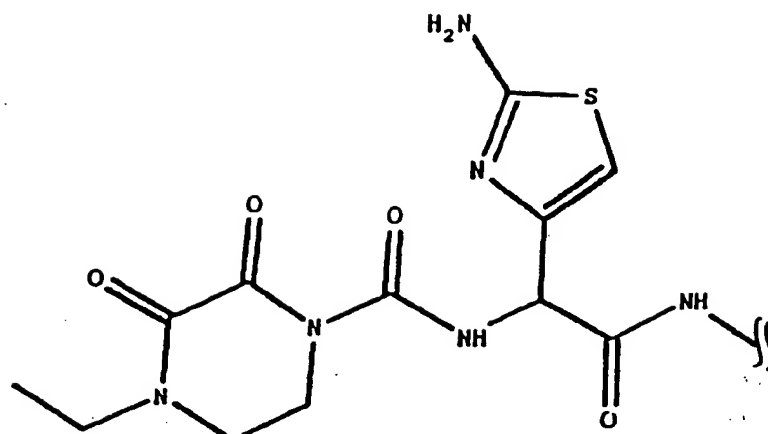
15

20

25

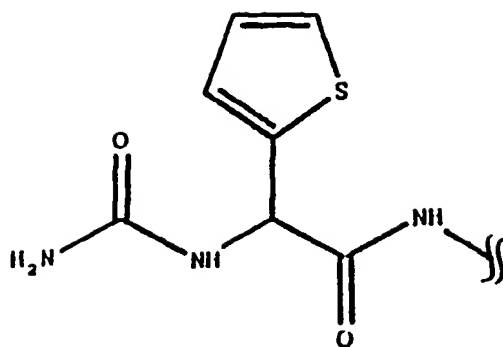
30

35



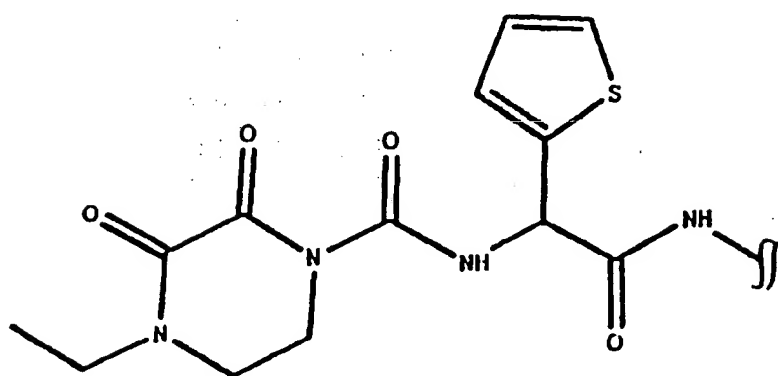
-31-

5



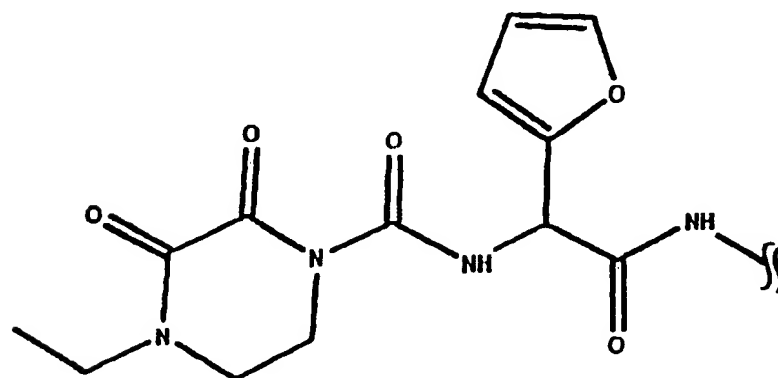
10

15



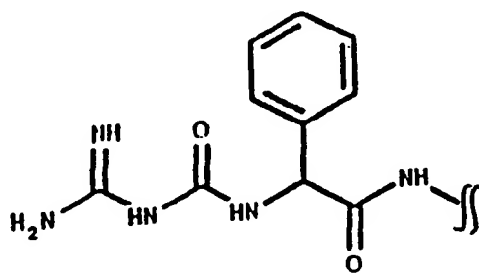
20

25



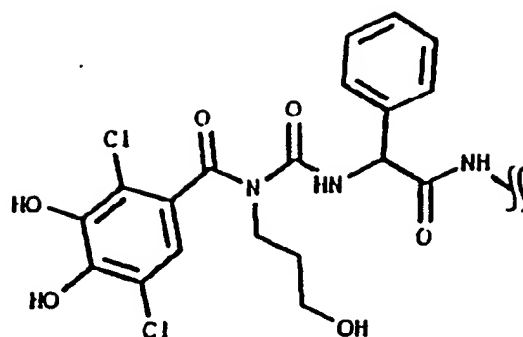
30

35



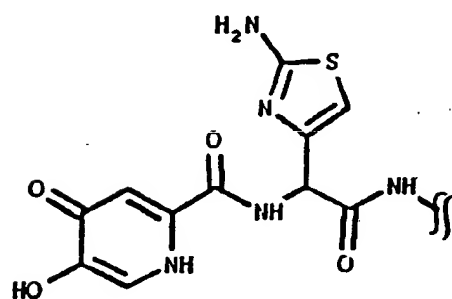
-32-

5



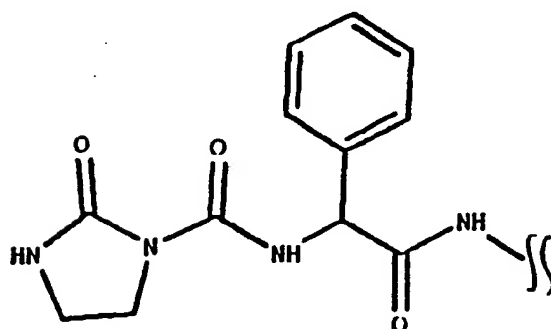
10

15



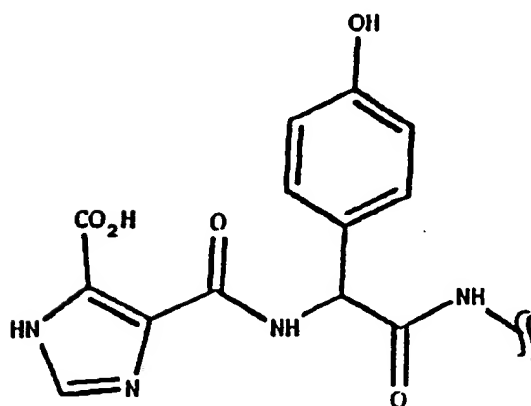
20

25



30

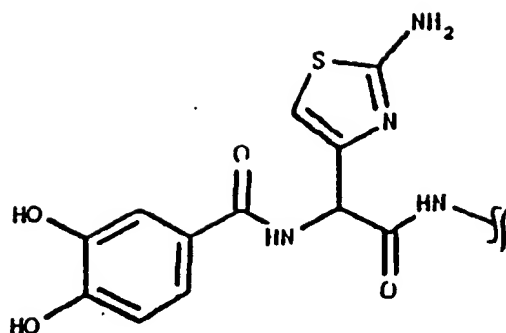
35



-33-

5

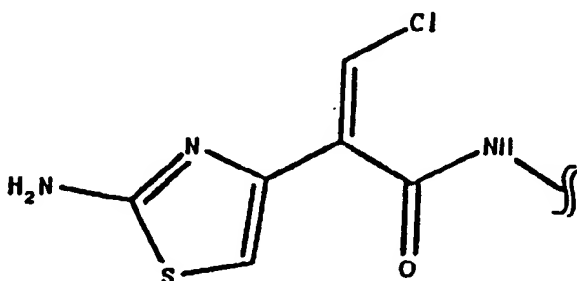
10



Another preferred R^1 group is $R^{12}-C(=CHR^{15})-C(=O)NH-$. Such groups include (for example) the following structures.

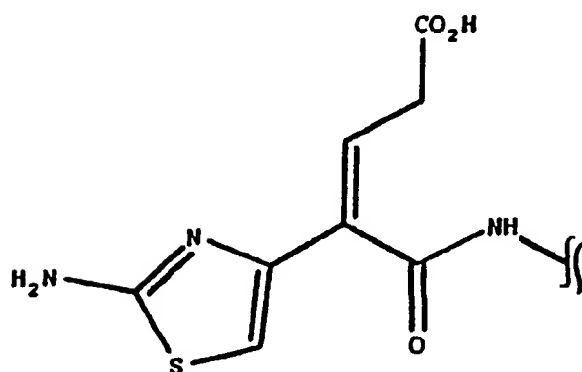
15

20



25

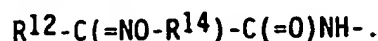
30



35

-34-

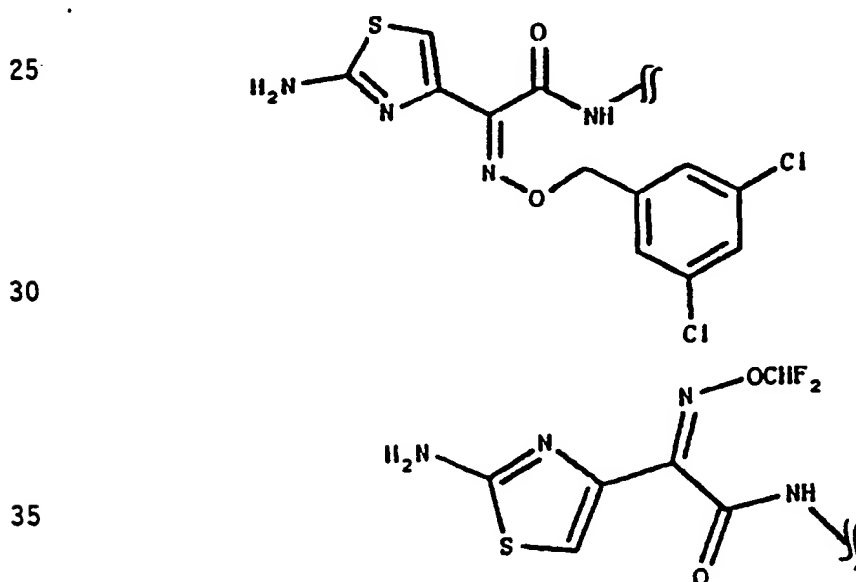
Another class of preferred R¹ groups (for lactam-containing moieties other than penems, carbapenems, clavams and clavams) include those of the formula:



5 Examples of this preferred class of R¹ groups include:

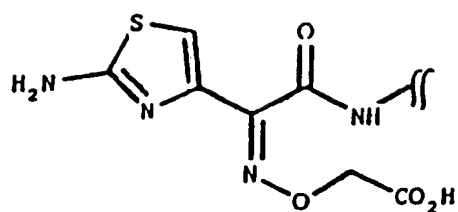
- 2-phenyl-2-hydroxyiminoacetyl;
 2-thienyl-2-methoxyiminoacetyl; and
 2-[4-(gamma-D-glutamyl)oxy]phenyl]-2-hydroxyiminoacetyl.
 (Z)-[[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino];
 10 [[(2-furanyl)(methoxyimino)acetyl]amino];
 (Z)-[[[(2-amino-4-thiazolyl)[(1-carboxy-1-methyl)ethoxyimino]acetyl]amino];
 (Z)-[[[(2-amino-4-thiazolyl)(1-carboxymethoxyimino)acetyl]amino];
 15 [[[(2-amino-4-thiazolyl)[(1H-imidazol-4-ylmethoxy)imino]acetyl]amino];
 (Z)-[[[(2-amino-4-thiazolyl-3-oxide)(methoxyimino)acetyl]amino]; and
 (S,Z)-[[[(2-amino-4-thiazolyl)[carboxy(3,4-dihydroxyphenyl)methoxyimino]acetyl]amino].
 20

Other preferred R¹ groups include the following structures.

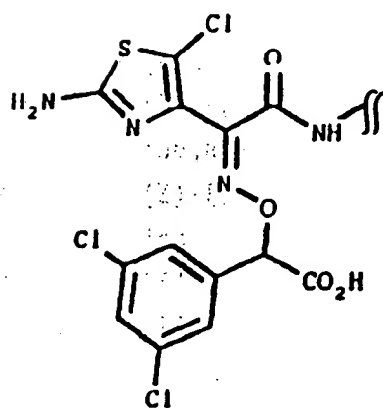


-35-

5

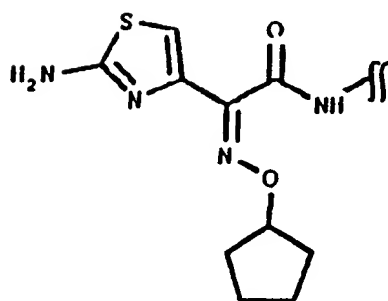


10



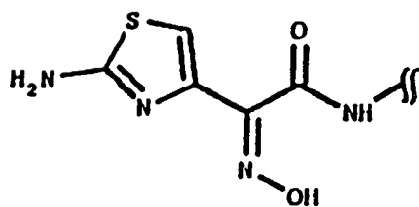
15

20



25

30



35

-36-

5

10

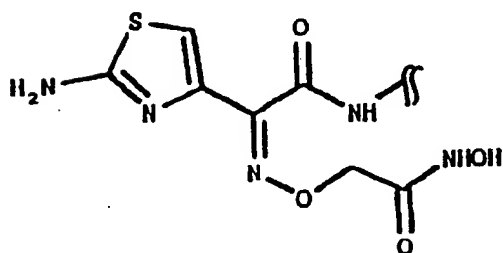
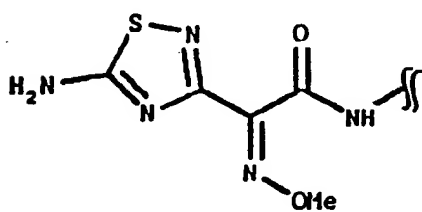
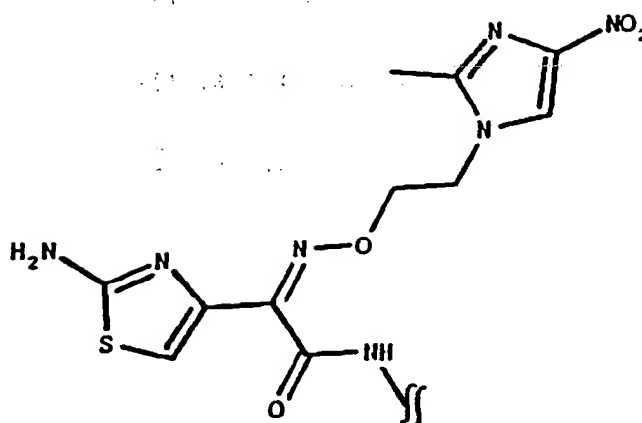
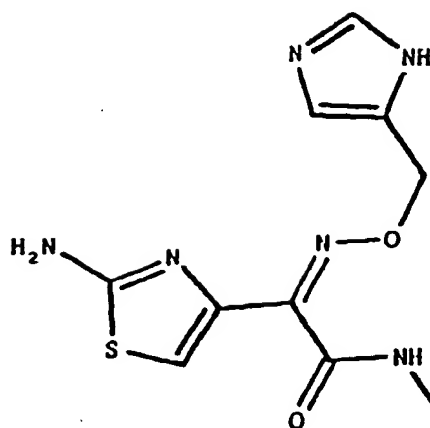
15

20

25

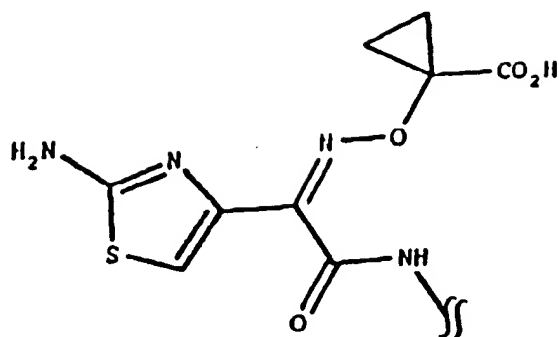
30

35

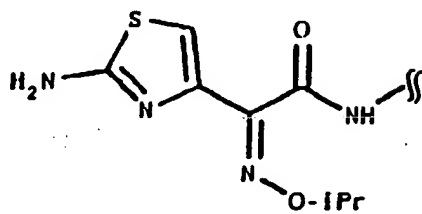


-37-

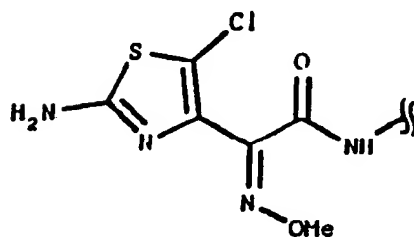
5



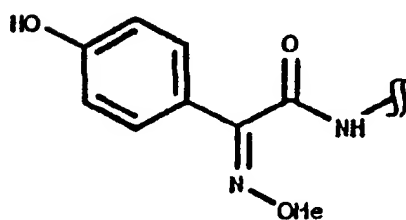
10



15



20



25

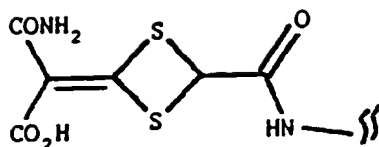
30

The following are other preferred R^1 groups.

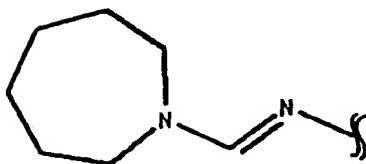
35

-38-

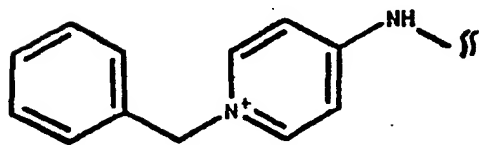
5



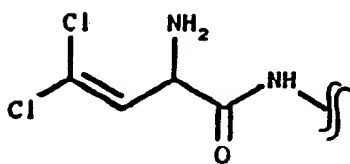
10



15



20



25

Suitable R² groups are among those well-known in the art, including those defined in the following documents (all incorporated by reference herein). W. Durckheimer et al., "Recent Developments in the Field of Beta-Lactam Antibiotics", 24 Angew. Chem. Int. Ed. Engl. 180 (1985); G. Rolinson, "Beta-Lactam Antibiotics", 17 J. Antimicrobial Chemotherapy 5 (1986); and European Patent Publication 187,456, Jung, published July 16, 1986. Preferred R² groups include hydrogen, methoxy,

-39-

ethoxy, propoxy, thiomethyl, halogen, cyano, formyl and formylamino. Particularly preferred R² groups include hydrogen, methoxy, halogen, and formylamino.

Quinolone Moieties:

5 Groups A¹, A², A³, R⁸, R⁷, and R⁹ form any of a variety of quinolone, naphthyridine or related heterocyclic moieties known in the art to have antimicrobial activity. Such moieties are well known in the art, as described in the following articles, all incorporated by reference herein: J. Wolfson et al., "The
10 Fluoroquinolones: Structures, Mechanisms of Action and Resistance, and Spectra of Activity In Vitro", 28 Antimicrobial Agents and Chemotherapy 581 (1985); and T. Rosen et al., 31 J. Med. Chem. 1586 (1988); T. Rosen et al., 31 J. Med. Chem. 1598 (1988); G. Klopman et al., 31 Antimicrob. Agents Chemother. 1831 (1987); 31:1831-1840; J. P. Sanchez et al., 31 J. Med. Chem. 983 (1988); J. M. Domagala et al., 31 J. Med. Chem. 991 (1988); M. P. Wentland et al., in 20 Ann. Rep. Med. Chem. 145 (D. M. Baily, editor, 1986); J. B. Cornett et al., in 21 Ann. Rep. Med. Chem. 139 (D. M. Bailey, editor, 1986); P. B. Fernandes et al., in 22
15 Ann. Rep. Med. Chem. 117 (D. M. Bailey, editor, 1987); R. Albrecht, 21 Prog. Drug Research 9 (1977); and P. B. Fernandes et al., in 23 Ann. Rep. Med. Chem. (R. C. Allen, editor, 1987).

 Preferred quinolone moieties include those where A¹ is C(R⁴⁰), A² is C(R⁶), and A³ is C(R⁴¹) (i.e., quinolones); A¹ is
25 nitrogen, A² is C(R⁶), and A³ is C(R⁴¹) (i.e., naphthyridines); A¹ is C(R⁴⁰), A² is C(R⁶), and A³ is nitrogen (i.e., cinnoline acid derivatives); and where A¹ is nitrogen, A² is nitrogen, and A³ is C(R⁴¹) (i.e., pyridopyrimidine derivatives). More preferred quinolone moieties are those where A¹ is C(R⁴⁰), A² is
30 C(R⁶), and A³ is C(R⁴¹) (i.e., quinolones); and where A¹ is nitrogen, A² is C(R⁶), and A³ is C(R⁴¹) (i.e., naphthyridines). Particularly preferred quinolone moieties are where A¹ is C(R⁴⁰), A² is C(R⁶), and A³ is C(R⁴¹) (i.e., quinolones).

 R⁸ is preferably alkyl, aryl, cycloalkyl and alkylamino.
35 More preferably, R⁸ is ethyl, 2-fluoroethyl, 2-hydroxyethyl, t-butyl, 4-fluorophenyl, 2,4-difluorophenyl, methylamino and

-40-

cyclopropyl. Cyclopropyl is a particularly preferred R⁸ group. Preferred quinolone moieties also include those where A¹ is C(R⁴⁰) and R⁸ and R⁴⁰ together comprise a 6-membered heterocyclic ring containing an oxygen or sulfur atom.

5 R⁶ is preferably hydrogen or halo. More preferably R⁶ is chlorine or fluorine. Fluorine is a particularly preferred R⁶ group.

Preferred R⁷ groups include nitrogen-containing heterocyclic rings. Particularly preferred are nitrogen-containing
10 heterocyclic rings having from 5 to 8 members. The heterocyclic ring may contain additional heteroatoms, such as oxygen, sulfur, or nitrogen, preferably nitrogen. Such heterocyclic groups are described in U.S. Patent 4,599,334, Petersen et al., issued July 8, 1986; and U.S. Patent 4,670,444, Grohe et al., issued
15 June 2, 1987 (both incorporated by reference herein). Preferred R⁷ groups include unsubstituted or substituted pyridine, piperidine, morpholine, diazabicyclo[3.1.1]heptane, diazabicyclo[2.2.1]heptane, diazabicyclo[3.2.1]octane, diazabicyclo[2.2.2]octane, thiazolidine, imidazolidine, pyrrole and thiamorpholine,
20 as well as the following particularly preferred R⁷ groups include piperazine, 3-methylpiperazine, 3-aminopyrrolidine, 3-aminomethylpyrrolidine, N,N-dimethylaminomethylpyrrolidine, N-methylaminomethylpyrrolidine, N-ethylaminomethylpyrrolidine, pyridine, N-methylpiperazine, and 3,5-dimethylpiperazine.

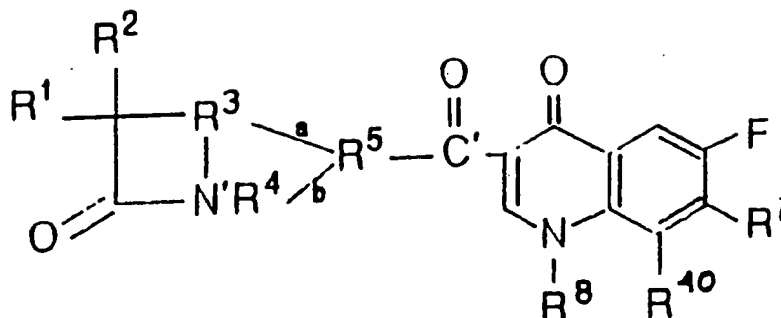
25 Preferred quinolonyl lactam esters include those having a 6-fluoroquinolone moiety or an 8-halo-6-fluoroquinolone moiety, of formula:

30

35

-41-

5



10

wherein A² is C(R⁶) and R⁶ is F; A³ is C(R⁴¹); and A¹ is C(R⁴⁰) where R⁴⁰ is hydrogen, fluorine or chlorine. Preferred examples of such quinolone moieties include:

15

1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid;

20

7-(3-aminopyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid;

7-[(3-aminomethyl)pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid;

7-(3-aminopyrrolidinyl)-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid;

7-(3-aminopyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid;

25

7-[(3-aminomethyl)pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid;

6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid;

30

1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid;

1-ethyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid;

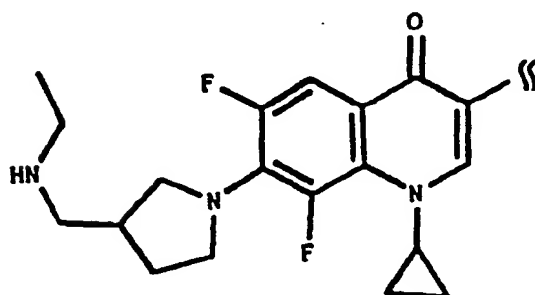
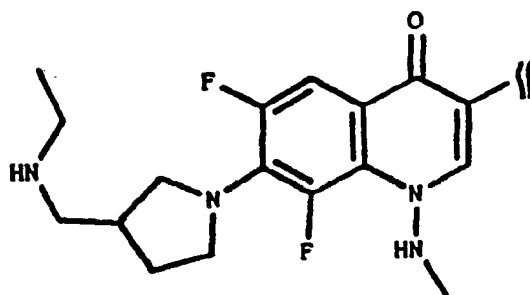
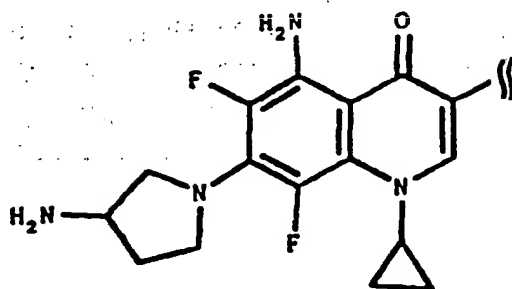
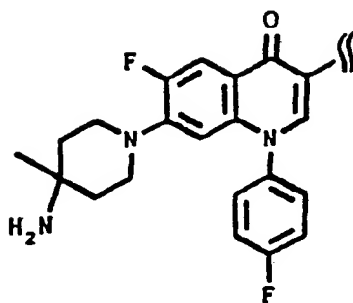
6-fluoro-1,4-dihydro-1-methylamino-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid; and

1-cyclopropyl-7-[3-(dimethylaminomethyl)-1-pyrrolidinyl]-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid;

35

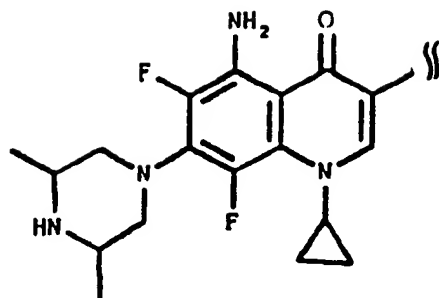
-42-

The following are other examples of such preferred quinolone moieties .

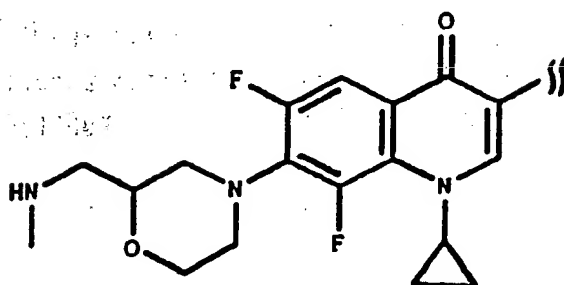


-43-

5

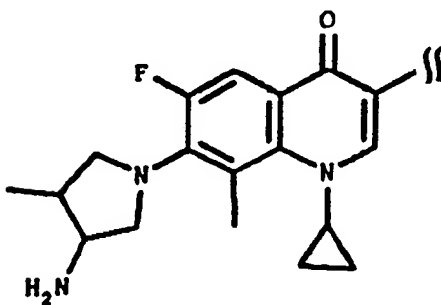


10



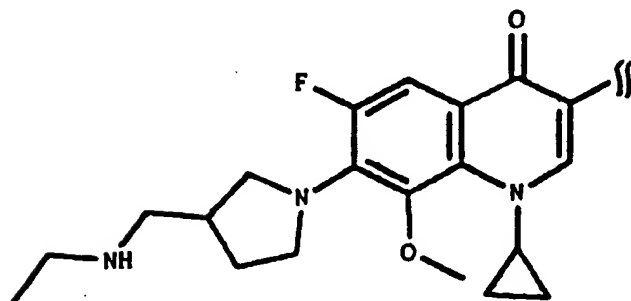
15

20



25

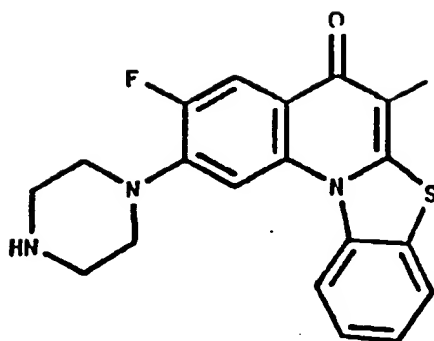
30



35

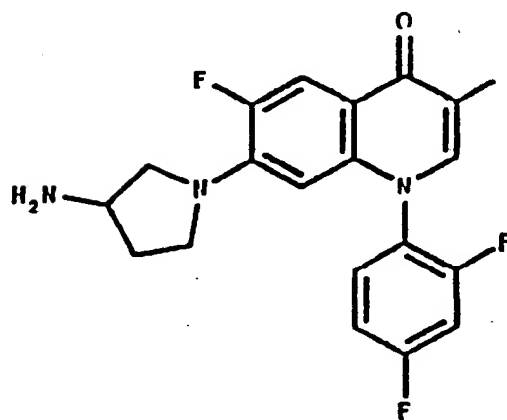
-44-

5



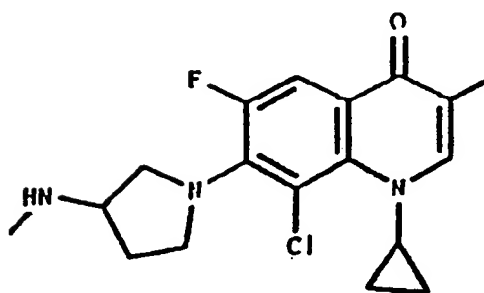
10

15



20

25

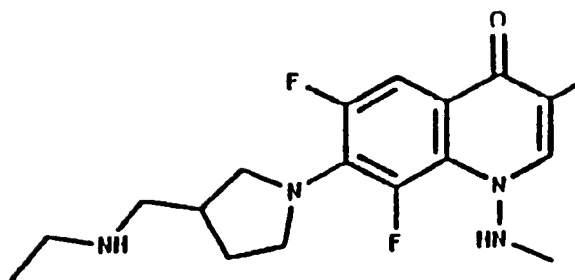


30

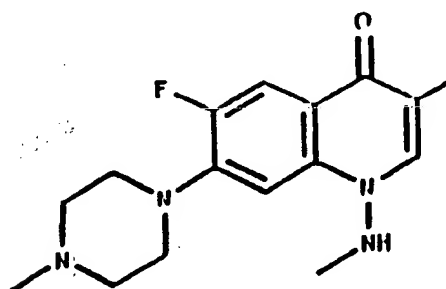
35

-45-

5

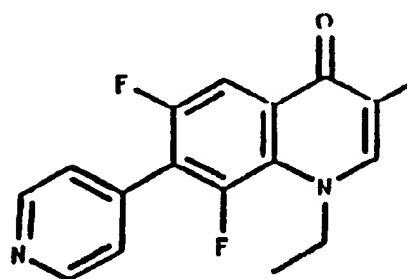


10



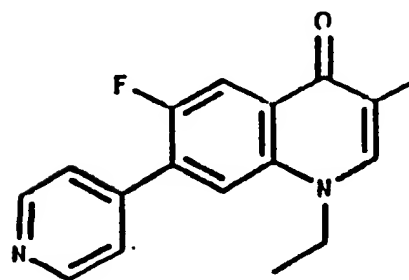
15

20



25

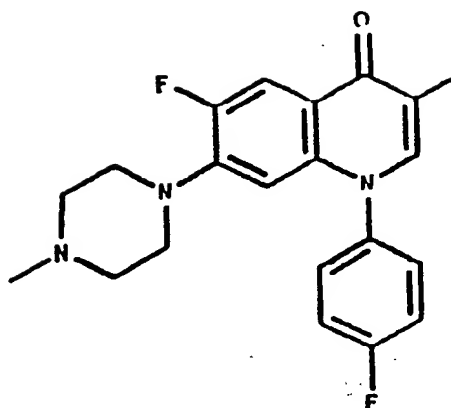
30



35

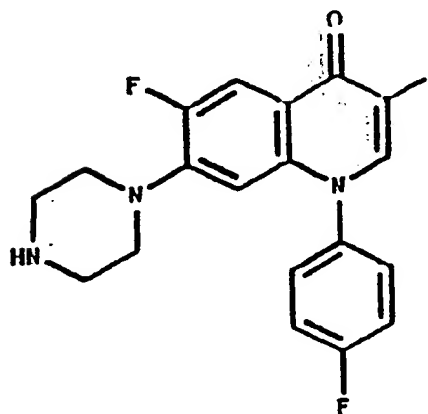
-46-

5



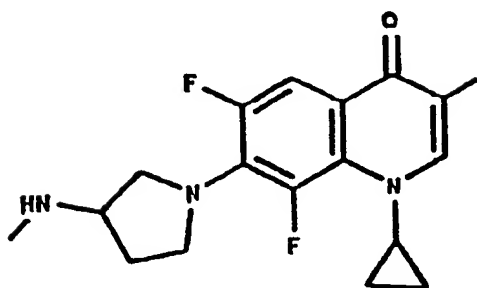
10

15



20

25

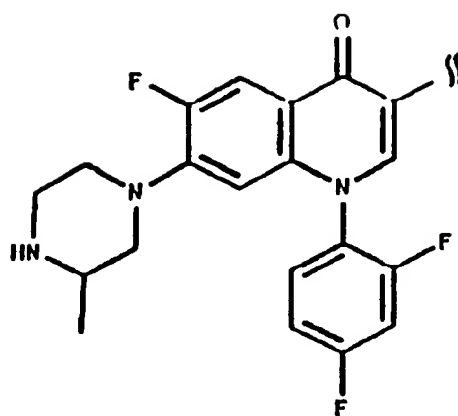


30

35

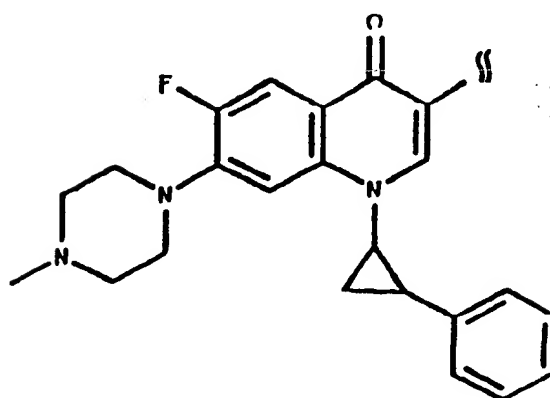
-47-

5



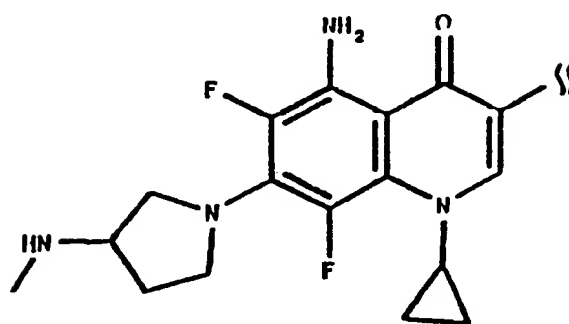
10

15



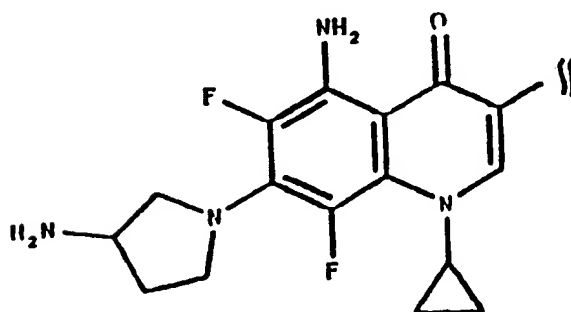
20

25



30

35



-48-

5

10

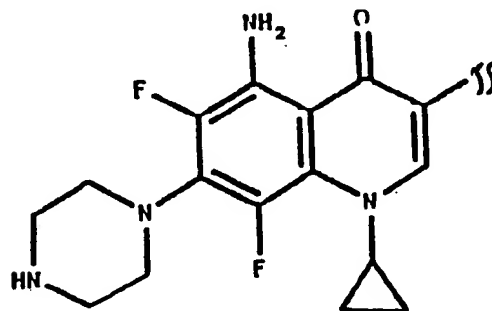
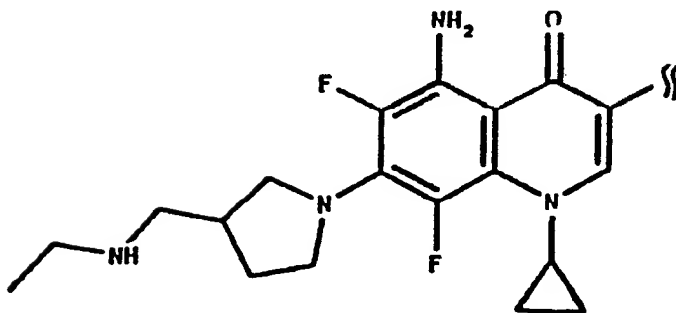
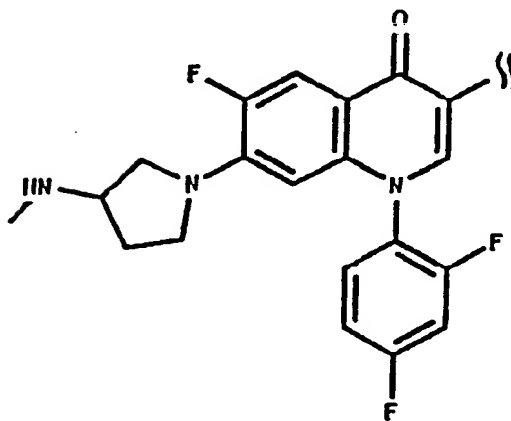
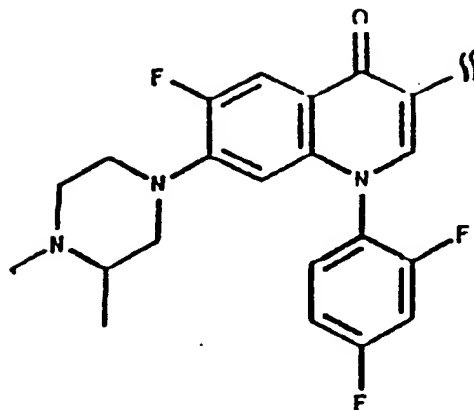
15

20

25

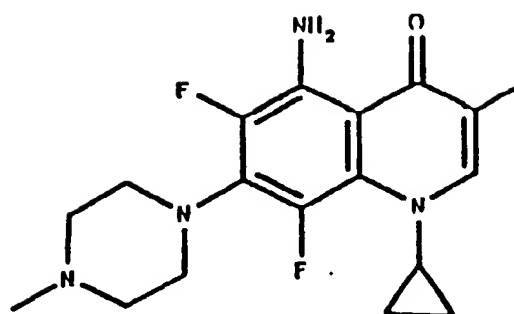
30

35



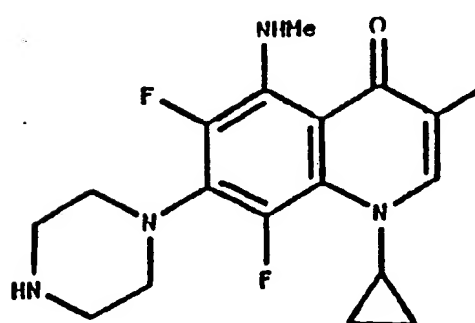
-49-

5



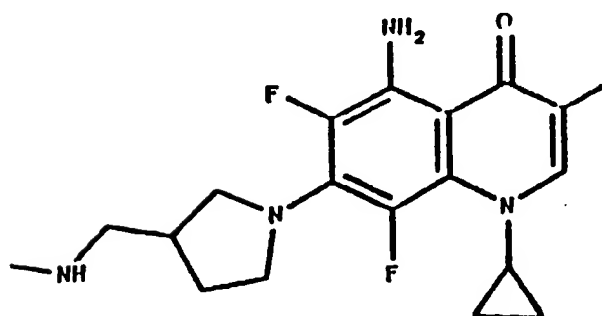
10

15



20

25

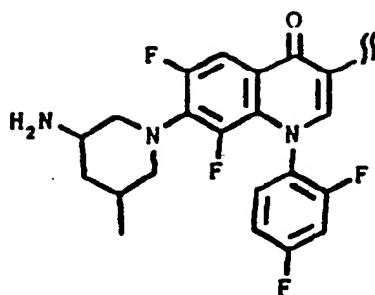


30

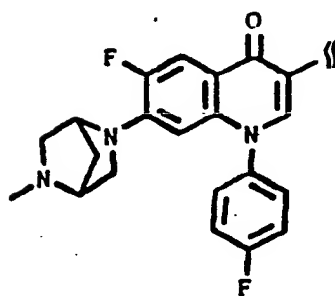
35

-50-

5

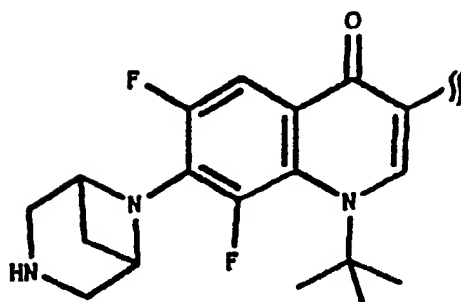


10



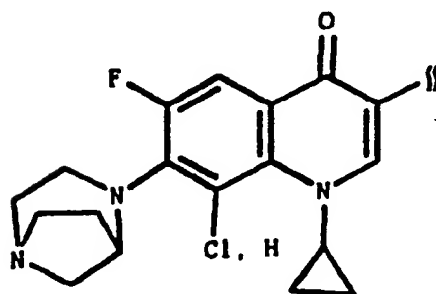
15

20



25

30



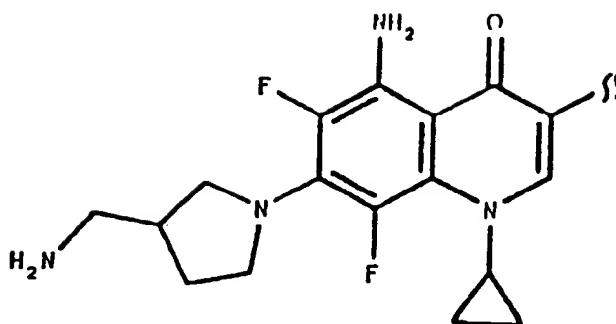
35

-51-

5

10

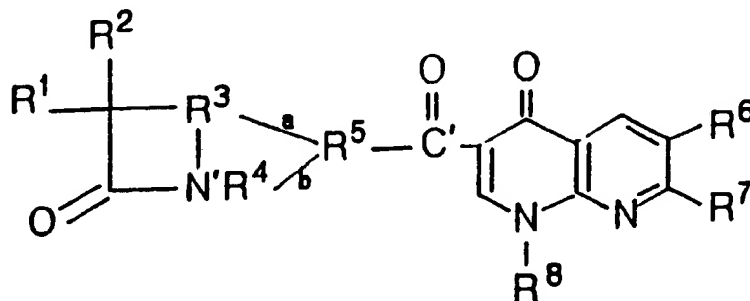
15



20

Also preferred are quinolonyl lactam esters having a 1,8-naphthyridine moiety, of formula:

25



30

wherein A¹ is N; A² is C(R⁶) and A³ is C(R⁴¹). Preferred examples of such quinolone moieties include:

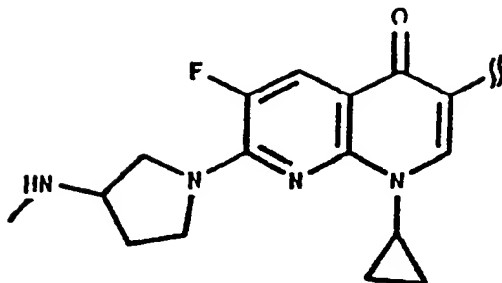
35

7-(3-aminopyrrolidinyl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid; and
1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-naphthyridine-3-carboxylic acid.

-52-

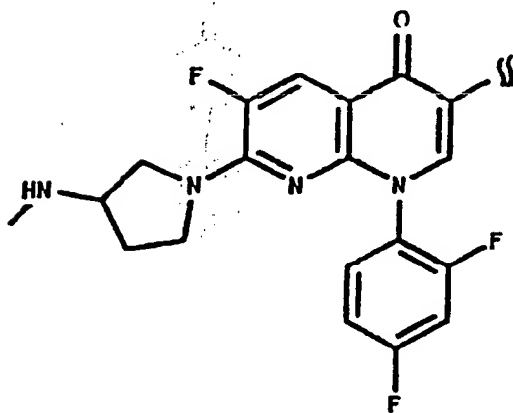
The following are other examples of such preferred quinolone moieties.

5



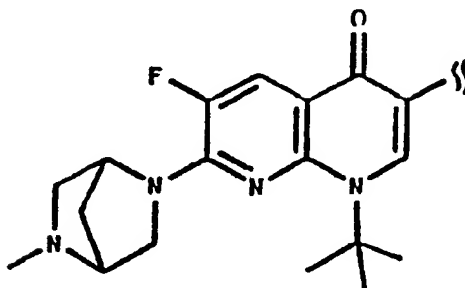
10

15



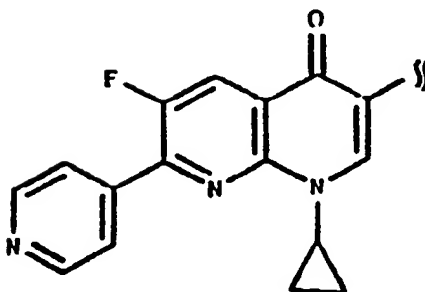
20

25



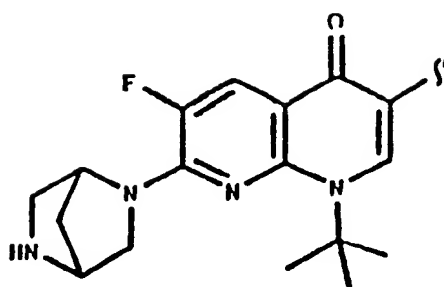
30

35

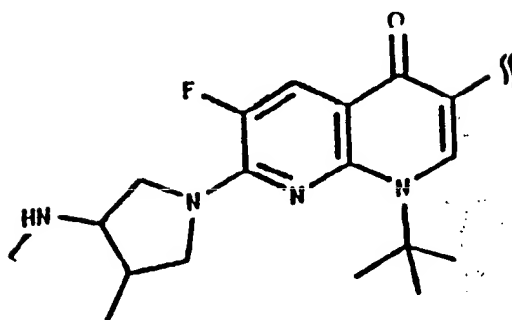


-53-

5

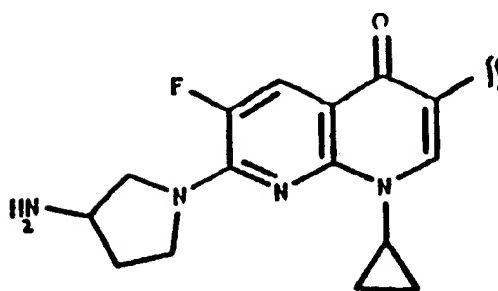


10

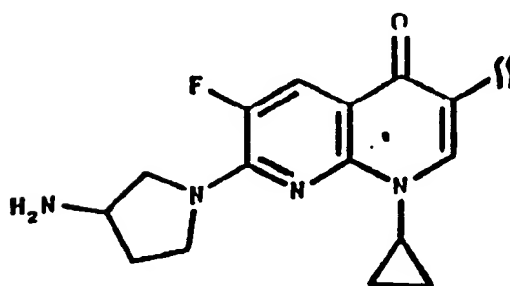


15

20

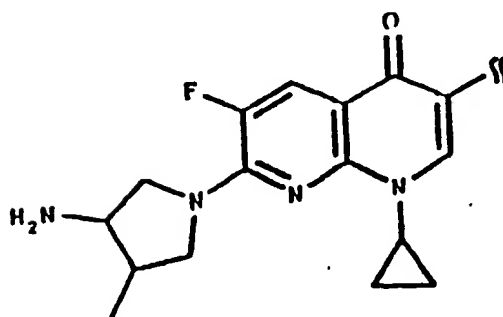


25



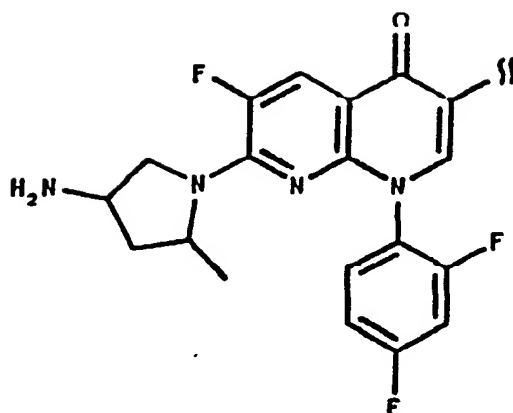
30

35



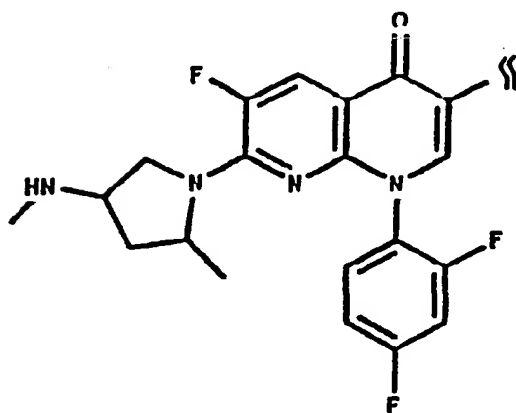
-54-

5



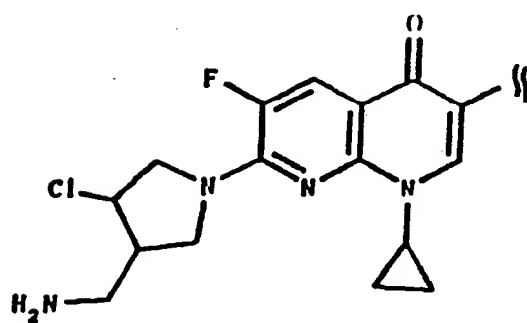
10

15



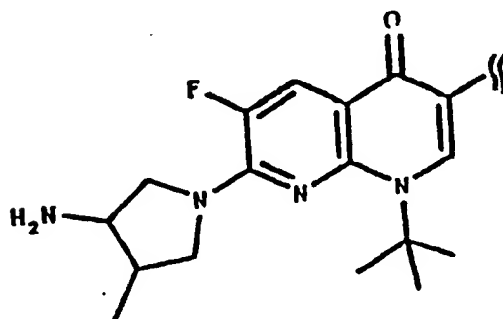
20

25



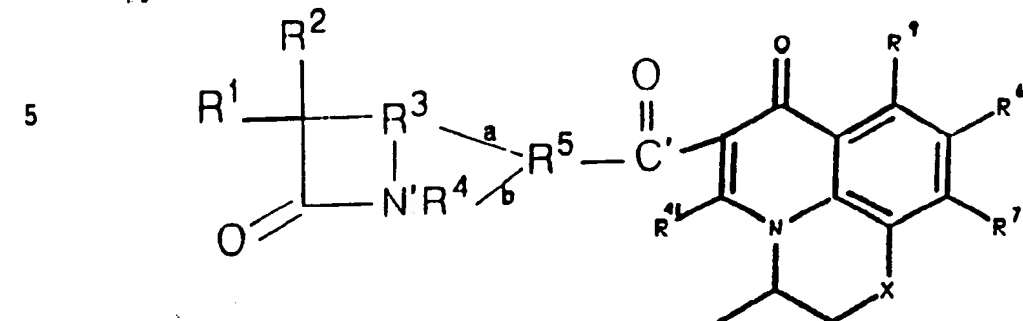
30

35



-55-

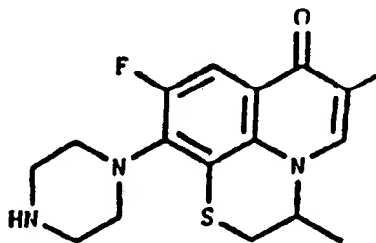
Also preferred are quinolonyl lactam esters having a pyridobenzoxazine or pyridobenzthiazine moiety, of formula:



wherein A¹ is C(R⁴⁰); A² is C(R⁶); A³ is C(R⁴¹); and R⁴⁰ and R⁸ together comprise a linking moiety between N' and A to form a 6-membered, oxygen-containing, heterocyclic ring where X (in this formula) is oxygen or sulfur. Preferred examples of such quinolone moieties include 9-fluoro-4,7-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid; and the following structures.

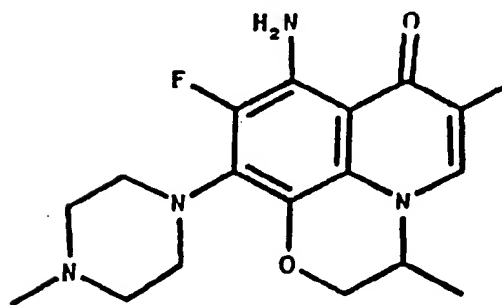
15

20



25

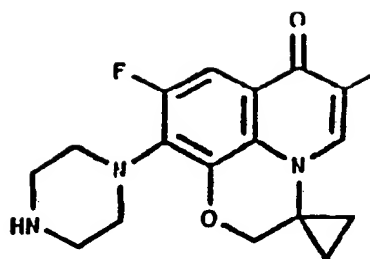
30



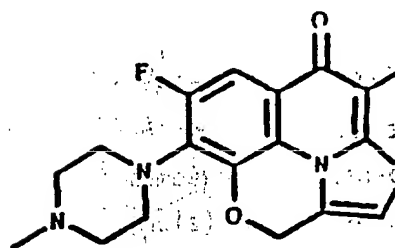
35

-56-

5

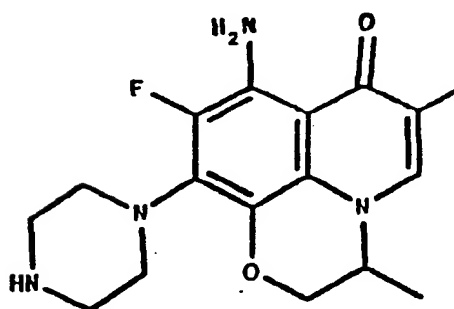


10



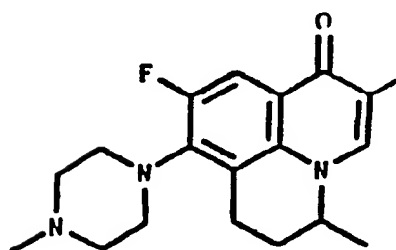
15

20



25

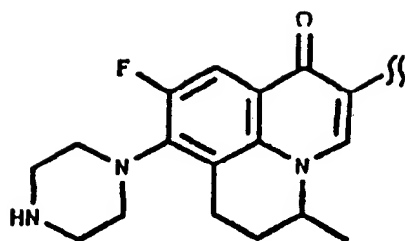
30



35

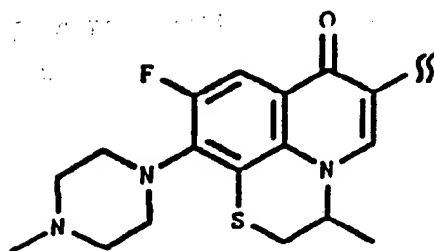
-57-

5



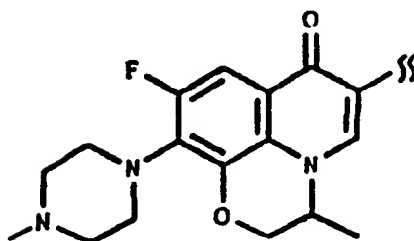
10

15



20

25



30

35

-58-

The specific physical, chemical, and pharmacological properties of the quinolonyl lactam esters of this invention may depend upon the particular combination of the integral lactam-containing moiety, quinolone moiety and linking moiety comprising the compound. For example, selection of particular integral moieties may affect the relative susceptibility of a quinolonyl lactam ester to bacterial resistance mechanisms (e.g., beta-lactamase activity).

Preferred quinolonyl lactam esters include compounds having the following specific combinations of lactam-containing moieties, quinolone moieties and linking moieties.

1) Ester-linked penem quinolones, such as compounds of the following classes.

a) where - the lactam-containing moiety is a penem, wherein bond "a" is a single bond; bond "b" is a double bond; R^3 is $-CH-$; R^4 is $-C(CO_2H)-$; R^5 is $-S-C''-CH_2-O-$; and
- the quinolone moiety is a structure, wherein A^2 is $-CF-$; A^3 is $-CH-$; and R^7 is a heterocyclic ring

b) where - the lactam-containing moiety is a penem, wherein bond "a" is a single bond; bond "b" is a double bond; R^1 is (1-hydroxyethyl); R^2 is $-H$; R^3 is $-CH-$; R^4 is $-C(CO_2H)-$; R^5 is $-S-C''-CH_2-O-$; and
- the quinolone moiety is a 6-fluoroquinolone moiety, wherein A^1 is $-C(R^{39})-$; A^2 is $-CF-$; A^3 is $-CH-$; and R^7 is a heterocyclic ring

c) where - the lactam-containing moiety is a penem, wherein referring to the formula, wherein bond "a" is a single bond; bond "b" is a double bond; R^3 is $-CH-$; R^4 is $-C(CO_2H)-$; R^5 is $-S-C''-CH_2-O-$;

-59-

- the quinolone moiety is a naphthyridinone, wherein A¹ is -N-; A² is -CF-; A³ is -CH-; and R⁷ is a heterocyclic ring

- 5 d) where - the lactam-containing moiety is a penem, wherein bond "a" is a single bond; bond "b" is a double bond; R³ is -CH-; R⁴ is -C(CO₂H)-; R⁵ is -S-C''-CH₂-O-; and
- 10 - the quinolone moiety is a structure, wherein A² is -CF-; A³ is -CH-; R⁹ is -H; A¹ is -CH-, -CF-, -CCl-, or -N-; R⁸ is cyclopropyl, ethyl, 2,4-difluorophenyl, 4-fluorophenyl, or t-butyl; and R⁷ is a 3-amino-1-pyrrolidinyl group, a 4-methyl-1-piperazinyl group, a 3-aminomethyl-1-pyrrolidinyl group, a 3-ethylaminomethyl-1-pyrrolidinyl group or a 1-piperazinyl group
- 15

20 Ester-linked penem quinolones of the classes (b), (c) and (d) are preferred; compounds of class (d) are particularly preferred.

3) Ester-linked penem quinolones, such as compounds of the following classes.

- 25 a) where - the lactam-containing moiety is a penem, wherein bond "a" is a single bond; bond "b" is a double bond; R³ is -CH-; R⁴ is -C(CO₂H)-; R⁵ is -S-C''-S-CH₂CH₂-O-; and
- 30 - the quinolone moiety is a structure, wherein A² is -CF-; A³ is -CH-; and R⁷ is a heterocyclic ring
- b) where - the lactam-containing moiety is a penem, wherein bond "a" is a single bond; bond "b" is a double bond; R³ is -CH-; R⁴ is -C(CO₂H)-; R⁵ is -S-C''-S-CH₂CH₂-O-; and
- 35

-60-

- the quinolone moiety is a 6-fluoroquinolone moiety, wherein A¹ is -C(R³⁹)-; A² is -CF-; A³ is -CH-; and R⁷ is a heterocyclic ring
- 5 c) where - the lactam-containing moiety is a penem, wherein bond "a" is a single bond; bond "b" is a double bond; R³ is -CH-; R⁴ is -C(CO₂H)-; R⁵ is -S-C''-S-CH₂CH₂-O-; and
 - the quinolone moiety is a naphthyridinone, wherein
- 10 A¹ is -N-; A² is -CF-; A³ is -CH-; and R⁷ is a heterocyclic ring
- d) where - the lactam-containing moiety is a penem, wherein bond "a" is a single bond; bond "b" is a double bond;
- 15 R¹ is (1-hydroxyethyl); R² is -H; R³ is -CH-; R⁴ is __; and
 - the quinolone moiety is a structure, wherein A² is -CF-; A³ is -CH-; R⁹ is -H; A¹ is -CH-, -CF-, -CCl-, or -N-; R⁸ is cyclopropyl, ethyl,
- 20 2,4-difluorophenyl, 4-fluorophenyl, or t-butyl; and R⁷ is a 3-amino-1-pyrrolidinyl group, a 4-methyl-1-piperazinyl group, a 3-aminomethyl-1-pyrrolidinyl group, a 3-ethylaminomethyl-1-pyrrolidinyl group or a
- 25 1-piperazinyl group

Ester-linked penem quinolones of the classes (b), (c) and (d) are preferred; compounds of class (d) are particularly preferred.

- 30 4) Ester-linked carbapenem quinolones, such as compounds of the following classes.

- a) where - the lactam-containing moiety is a carbapenem, wherein bond "a" is a single bond; bond "b" is a
- 35 double bond; R³ is -CH-; R⁴ is -C(CO₂H)-; R⁵ is -CH(R³³)-C''-CH₂-O-; and

-61-

- the quinolone moiety is a structure, wherein A² is -CF-; A³ is -CH-; and R⁷ is a heterocyclic ring
- 5 b where - the lactam-containing moiety is a carbapenem, wherein bond "a" is a single bond; bond "b" is a double bond; R³ is -CH-; R⁴ is -C(CO₂H)-; R⁵ is -CH(R³³)-C''-CH₂-O-; and
- 10 - the quinolone moiety is a 6-fluoroquinolone moiety, wherein A¹ is -C(R³⁹)-; A² is -CF-; A³ is -CH-; and R⁷ is a heterocyclic ring
- 15 c) where - the lactam-containing moiety is a carbapenem, wherein bond "a" is a single bond; bond "b" is a double bond; R³ is -CH-; R⁴ is -C(CO₂H)-; R⁵ is -CH(R³³)-C''-CH₂-O-; and
- 20 - the quinolone moiety is a naphthyridinone, wherein A¹ is -N-; A² is -CF-; A³ is -CH-; and R⁷ is a heterocyclic ring
- 25 d) where - the lactam-containing moiety is a carbapenem, wherein bond "a" is a single bond; bond "b" is a double bond; R¹ is (1-hydroxyethyl); R² is -H; R³ is -CH-; R⁴ is -C(CO₂H)-; R⁵ is -CH(R³³)-C''-CH₂-O-; R³³ is -H or -Me; and
- 30 - the quinolone moiety is a structure, wherein A² is -CF-; A³ is -CH-; R⁹ is -H; A¹ is -CH-, -CF-, -CCl-, or -N-; R⁸ is cyclopropyl, ethyl, 2,4-difluorophenyl, 4-fluorophenyl, or t-butyl; and R⁷ is a 3-amino-1-pyrrolidinyl group, a 4-methyl-1-piperazinyl group, a 3-aminomethyl-1-pyrrolidinyl group, a 3-ethylaminomethyl-1-pyrrolidinyl group or a 1-piperazinyl group
- 35

-62-

Ester-linked carbapenem quinolones of the classes (b), (c) and (d) are preferred; compounds of class (d) are particularly preferred.

5 5) Ester-linked carbapenem quinolones, such as compounds of the following classes.

10 a) where - the lactam-containing moiety is a carbapenem, wherein bond "a" is a single bond; bond "b" is a double bond; R³ is -CH-; R⁴ is -C(CO₂H)-; R⁵ is -CH(R³³)-C''-S-CH₂CH₂-O-; and

the quinolone moiety is a structure, wherein A² is -CF-; A³ is -CH-; and R⁷ is a heterocyclic ring

15 b) where - the lactam-containing moiety is a carbapenem, wherein bond "a" is a single bond; bond "b" is a double bond; R³ is -CH-; R⁴ is -C(CO₂H)-; R⁵ is -CH(R³³)-C''-S-CH₂CH₂-O-; and

20 - the quinolone moiety is a 6-fluoroquinolone moiety, wherein A¹ is -C(R³⁹)-; A² is -CF-; A³ is -CH-; and R⁷ is a heterocyclic ring

25 c) where - the lactam-containing moiety is a carbapenem, wherein bond "a" is a single bond; bond "b" is a double bond; R³ is -CH-; R⁴ is -C(CO₂H)-; R⁵ is -CH(R³³)-C''-S-CH₂CH₂-O-; and

30 - the quinolone moiety is a naphthyridinone, wherein A¹ is -N-; A² is -CF-; A³ is -CH-; and R⁷ is a heterocyclic ring

35 d) where - the lactam-containing moiety is a carbapenem, wherein bond "a" is a single bond; bond "b" is a double bond; R¹ is (1-hydroxyethyl); R² is -H; R³ is -CH-; R⁴ is -C(CO₂H)-; R⁵ is -CH(R³³)-C''-S-CH₂CH₂-O-; R³³ is -H or -Me; and

-63-

- the quinolone moiety is a structure, wherein A² is -CF-; A³ is -CH-; R⁹ is -H; A¹ is -CH-, -CF-, -CCl-, or -N-; R⁸ is cyclopropyl, ethyl, 2,4-difluorophenyl, 4-fluorophenyl, or t-butyl; and R⁷ is a 3-amino-1-pyrrolidinyl group, a 4-methyl-1-piperazinyl group, a 3-aminomethyl-1-pyrrolidinyl group, a 3-ethylaminomethyl-1-pyrrolidinyl group or a 1-piperazinyl group.

10

Ester-linked penem quinolones of the classes (b), (c) and (d) are preferred; compounds of class (d) are particularly preferred.

15.

6) Ester-linked oxacephem quinolones, such as compounds of the class where

20

- the lactam-containing moiety is a oxacephem, wherein bond "a" is a single bond; bond "b" is a double bond; R³ is -CH-; R⁴ is -C(CO₂H)-; R⁵ is -O-CH₂-C''-CH₂-O-;
- the quinolone moiety is a structure, wherein A² is -CF-; A³ is -CH-; and R⁷ is a heterocyclic ring.

25

7) Ester-linked isocephem quinolones, such as compounds of the class where

30

- the lactam-containing moiety is a isocephem, wherein bond "a" is a single bond; bond "b" is a double bond; R³ is -CH-; R⁴ is -C(CO₂H)-; R⁵ is -CH₂-S-C''-CH₂-O-; and
- the quinolone moiety is a structure, wherein A² is -CF-; A³ is -CH-; and R⁷ is a heterocyclic ring.

35

8) Ester-linked iso-oxacephem quinolones, such as compounds of the class where

-64-

- the lactam-containing moiety is a iso-oxacephem, wherein bond "a" is a single bond; bond "b" is a double bond; R³ is -CH-; R⁴ is -C(CO₂H)-; R⁵ is -CH₂-O-C''-CH₂-O-; and
- 5 - the quinolone moiety is a structure, wherein A² is -CF-; A³ is -CH-; and R⁷ is a heterocyclic ring.

9) Ester-linked carbacephem quinolones, such as compounds of the class where

- 10 - the lactam-containing moiety is a carbacephem, wherein bond "a" is a single bond; bond "b" is a double bond; R³ is -CH-; R⁴ is -C(CO₂H)-; R⁵ is -CH₂-CH₂-C''-CH₂-O-; and
- 15 - the quinolone moiety is a structure, wherein A² is -CF-; A³ is -CH-; and R⁷ is a heterocyclic ring.

10) Ester-linked monobactam quinolones, such as compounds of the following classes.

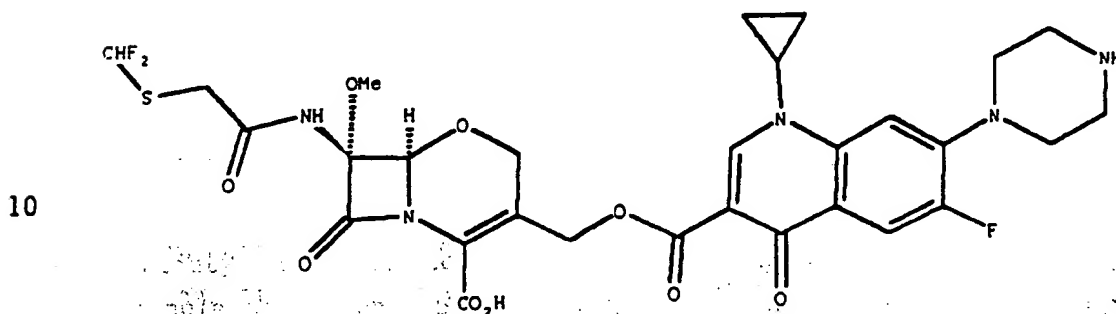
- 20 a) where - the lactam-containing moiety is a monobactam, wherein bond "a" is a single bond; bond "b" is nil; R³ is -CH- and is bonded directly to X; R⁵ is nil; X is -CH₂O-; and
- 25 - the quinolone moiety is a structure, wherein A² is -CF-; A³ is -CH-; and R⁷ is a heterocyclic ring
- 30 b) where - the lactam-containing moiety is a monobactam, wherein bond "a" is a single bond; bond "b" is nil; R³ is -CH- and is bonded directly to X; R⁵ is nil; X is -O-; and
- 35 - the quinolone moiety is a structure, wherein A² is -CF-; A³ is -CH-; and R⁷ is a heterocyclic ring

Quinolonyl lactams esters of this invention include (for example) the following compounds.

-65-

[6R-(6 α ,7 β)]-7-[[[(Difluoromethyl)thio]acetyl]amino]-7-methoxy]-
 3-[[[1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-
 3quinolinyl]carbonyloxy]methyl]-8-oxo-5-oxa-1-azabicyclo[4.2.0]-
 oct-2-ene-2-carboxylic acid

5

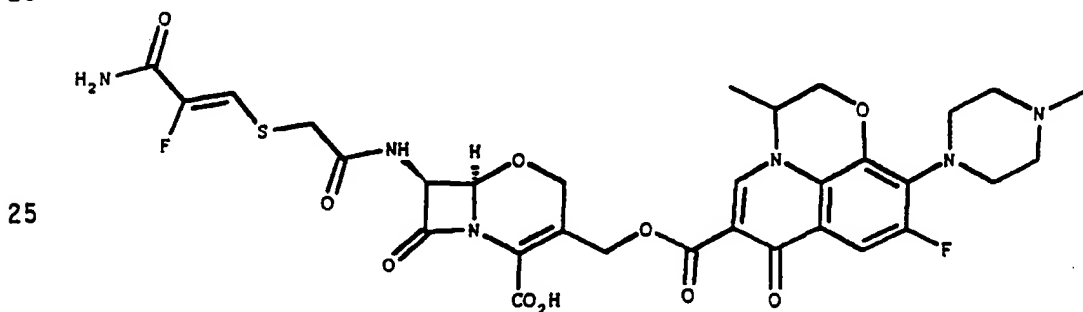


10

[6R-(6 α ,7 β)]-7-[[[(2-Aminocarbonyl-2-fluoroethenyl)thio]acetyl]
 amino]-3-[[[9-fluoro-3,7-dihydro-3-methyl-10-(4-methyl-1-
 piperazinyl)-7-oxo-2H-pyrido[1,2,3-de]-1,4-benzoxazin-6-yl]-
 carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-
 2-carboxylic acid

15

20



25

30

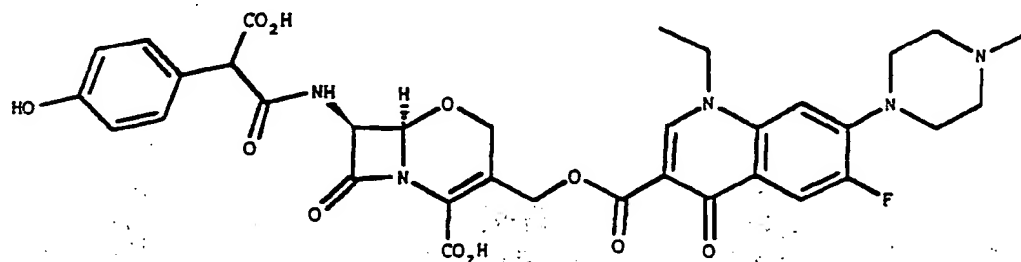
35

-66-

[6R-[6 α ,7 β]]-7-[[Carboxy(4-hydroxyphenyl)acetyl]amino]-3-[[[1-ethyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinyl]carbonyloxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

5

10

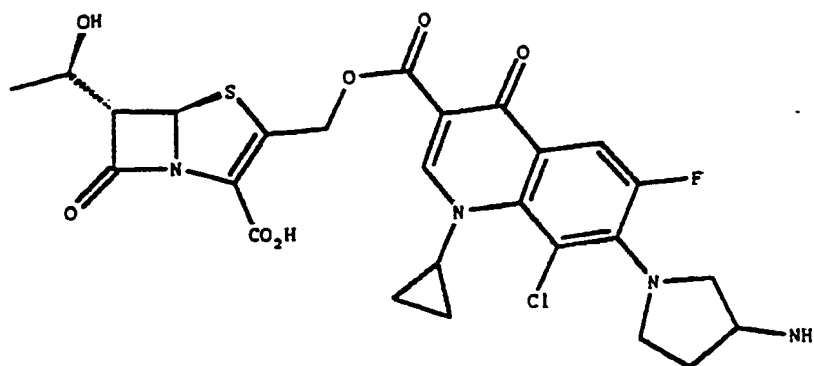


15

[5R-[5 α ,6 α]]-3-[[[7-(3-Aminopyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinyl]carbonyloxy]methyl]-6-[(R)-1-hydroxyethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

20

25

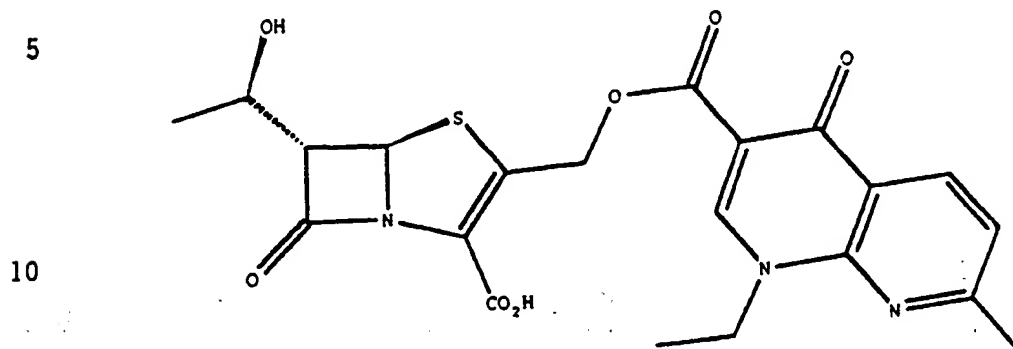


30

35

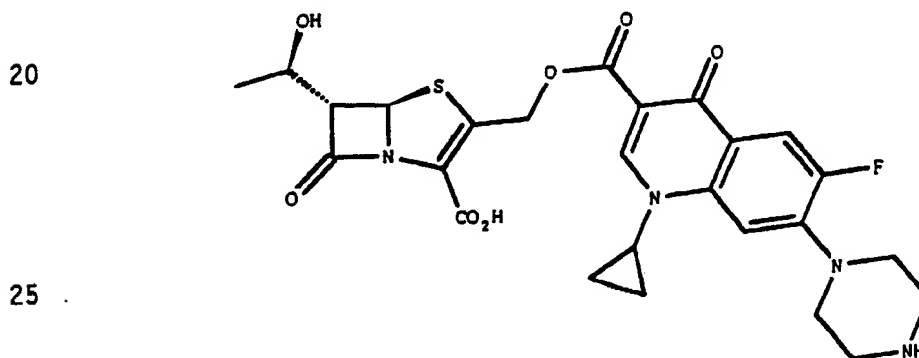
-67-

[5R-[5 α ,6 α]]-3-[[[1-Ethyl-1,4-dihydro-6-methyl-4-oxo-1,8-naphthyridin-3-yl]carbonyloxy]methyl]-6-[(R)-1-hydroxyethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid



15

[5R-[5 α ,6 α]]-3-[[[1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoliny]carbonyloxy]methyl]-6-[(R)-1-hydroxyethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]oct-2-ene-2-carboxylic acid



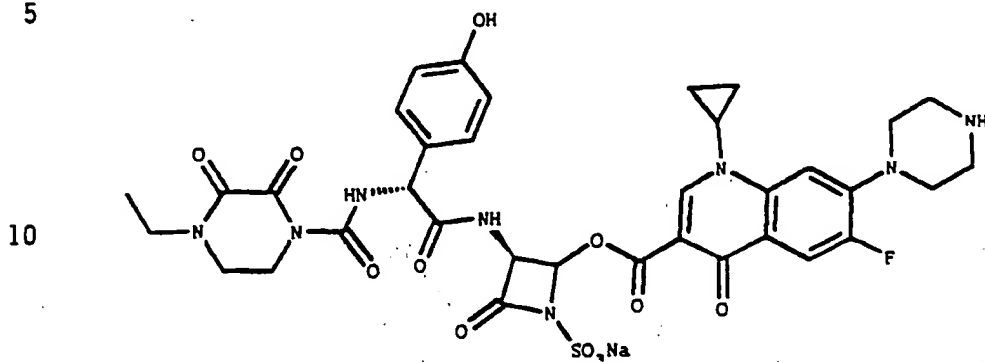
30

35

-68-

(3S)-2-[[[1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoliny]carbonyloxy]-3-[[[[(R)-4-ethyl-2,3-dioxo-1-piperazinyl]carbonyl]amino](4-hydroxyphenyl)acetyl]amino]-4-oxo-1-azetidinesulfonic acid sodium salt

5



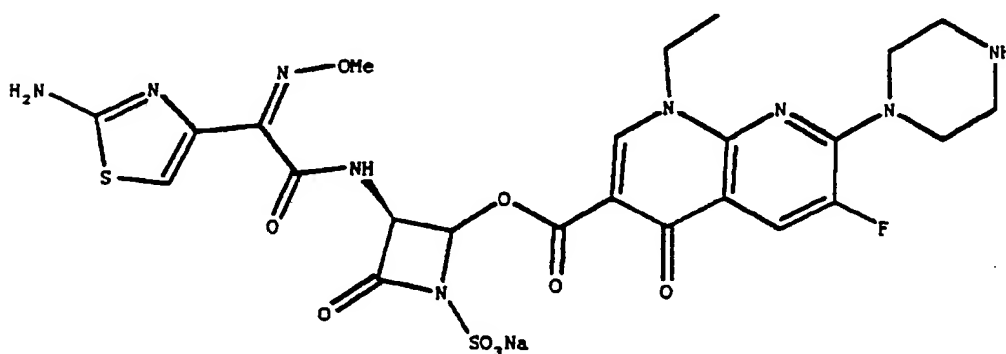
10

(3S)-3-[[[(2-Amino-4-thiazolyl)(methoxyimino)acetyl]amino]-2-[[[1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-naphthyridin-3-yl]carbonyloxy]-4-oxo-1-azetidinesulfonic acid sodium salt

15

20

25

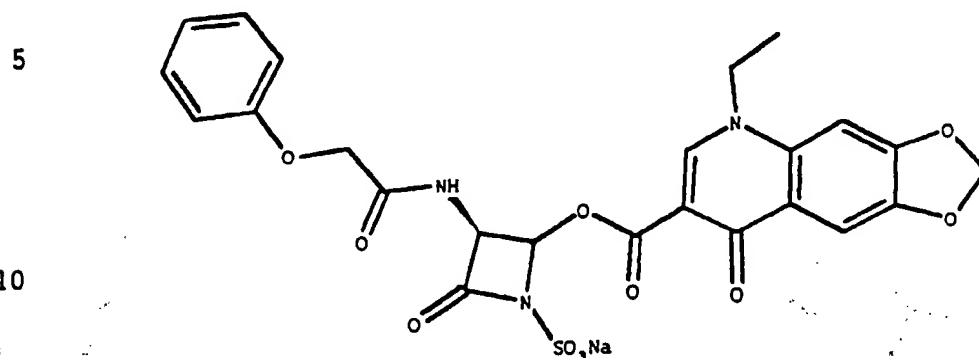


30

35

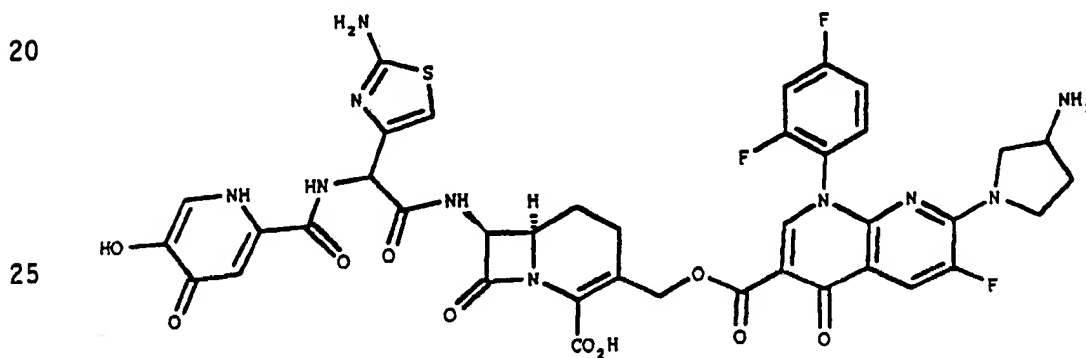
-69-

(3S)-2-[[5-Ethyl-5,8-dihydro-8-oxo-1,3-dioxolo[4,5-g]7-quinoliny]carbonyloxy]-4-oxo-3-[(phenoxyacetyl)amino]azetidinesulfonic acid sodium salt



15

[6R-[6 α ,7 β]]-3-[[[7-(3-Amino-1-pyrrolidiny)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridin-3-yl]carbonyloxy]methyl]-7-[[[(5-hydroxy-4-oxo-1(4H)-pyridin-2-yl)carbonyl]amino](2-amino-4-thiazolyl)acetyl]amino]-8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

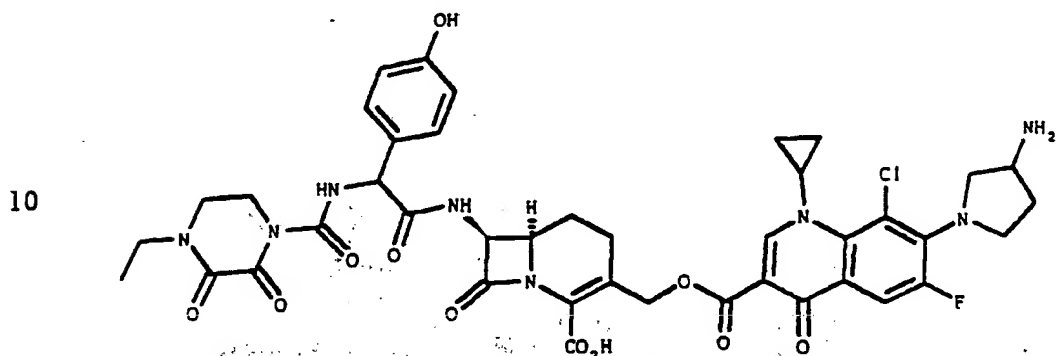


30

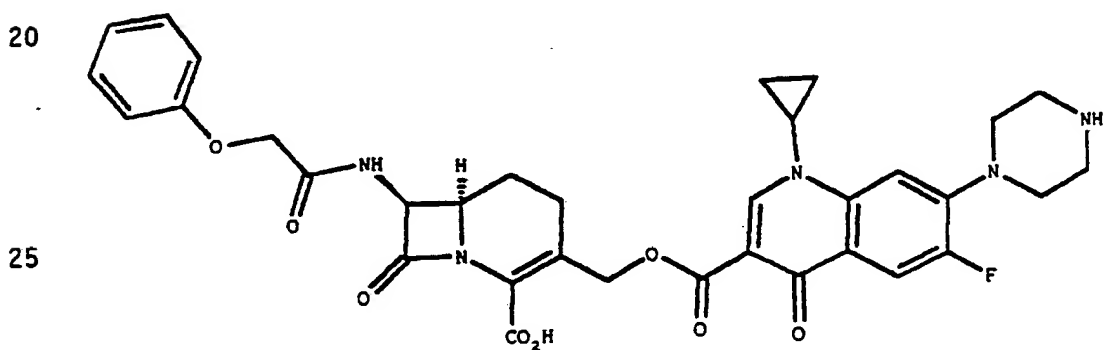
35

-70-

[6R-[6 α ,7 β]]-3-[[[7-(3-Amino-1-pyrrolidinyl)-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinyl]carbonyloxy]-methyl]-7-[[[[(R)-4-ethyl-2,3-dioxo-1-piperazinyl]carbonyl]-amino](4-hydroxyphenyl)acetyl]amino]-8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid



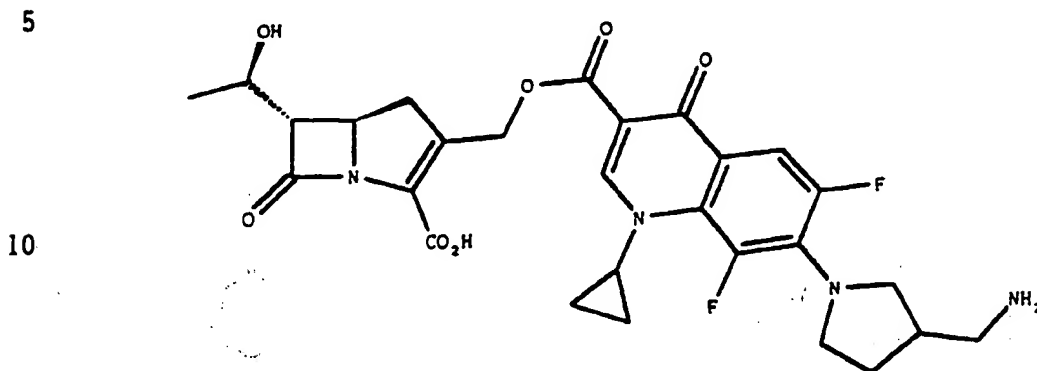
[6R-[6 α ,7 β]]-3-[[[1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinyl]carbonyloxy]methyl]-7-[[phenoxyacetyl]amino]-8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid



35

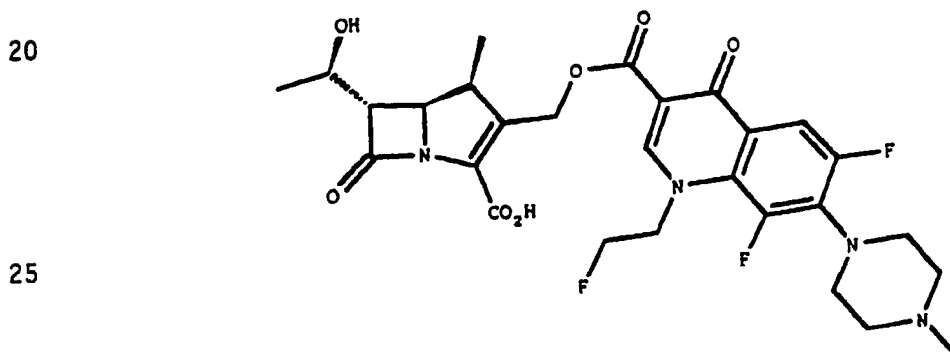
-71-

[5R, (5 α , 6 α)]-3-[[[7-[3-(Aminomethyl)-1-pyrrolidinyl]-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinyl]carbonyl]oxy]methyl]-6-[(R)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid



15

[5R, (5 α , 6 α)]-3-[[[6,8-Difluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxo-7-(4-methyl-1-piperazinyl)-3-quinolinyl]carboxyl]oxy]methyl]-6-[(R)-1-hydroxyethyl]-4 β -methyl-7-oxo-1-azabicyclo [3.2.0]hept-2-ene-2-carboxylic acid

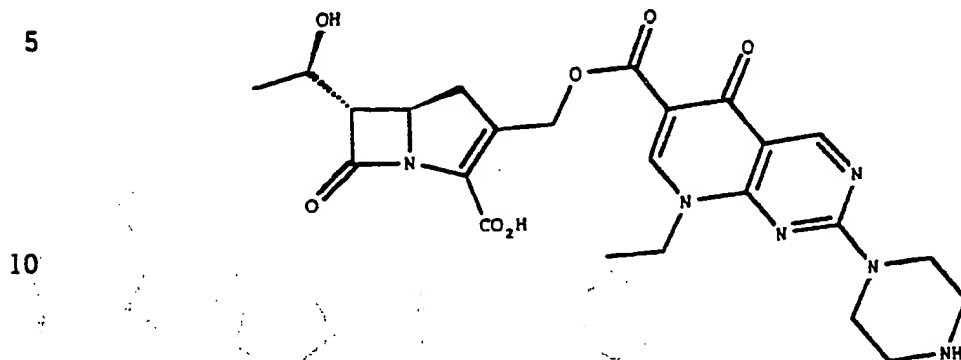


30

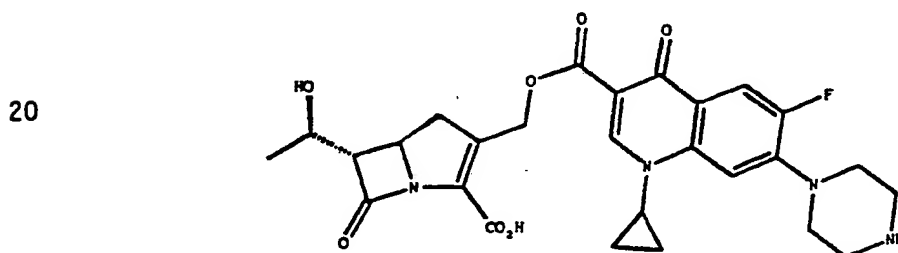
35

-72-

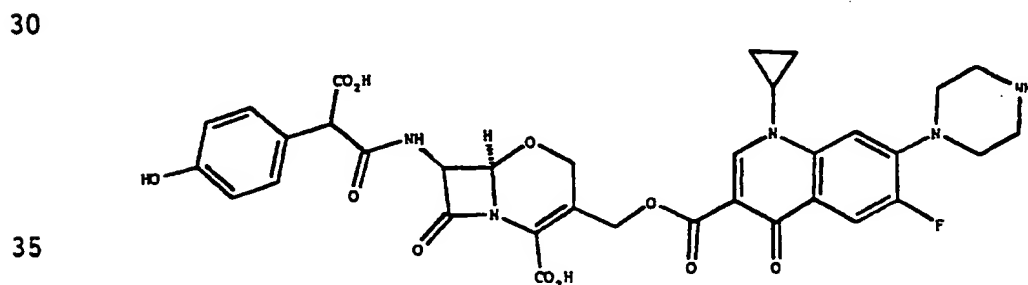
[5R, (5 α , 6 α)]-3-[[[8-Ethyl-5,8-dihydro-5-oxo-2-(1-piperazinyl)pyrido[2,3-d]pyrimidinyl]carbonyloxy]methyl]-6-[(R)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid



15 [5R, [5 α , 6 α]]-3-[[[1-Cyclopropyl-6-fluoro-1,4-dihydro-7-(1-piperazinyl)-4-oxo-3-quinoliny]carbonyloxy]methyl]-6-[(R)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid



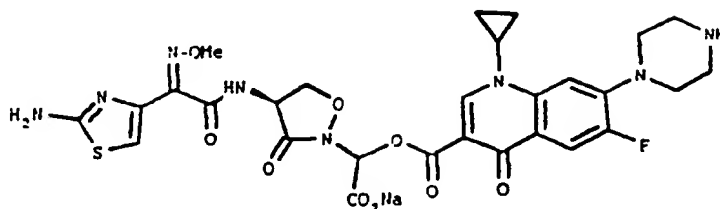
25 [6R-[6 α , 7 β]]-7-[[Carboxy(4-hydroxyphenyl)acetyl]amino]-3-[[[1-cyclopropyl-6-fluoro-1,4-dihydro-7-(1-piperazinyl)-4-oxo-3-quinoliny]carbonyloxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid



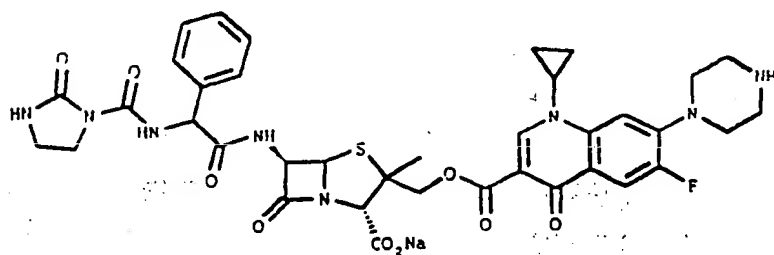
-73-

Other preferred quinolonyl lactam esters are exemplified by the following structures.

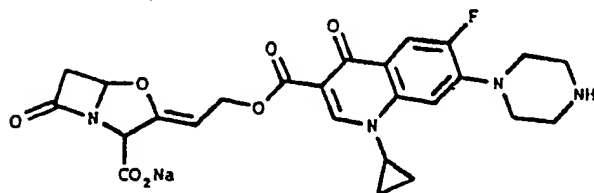
5



10

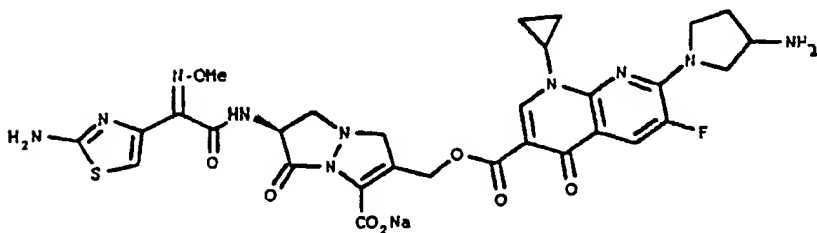


15

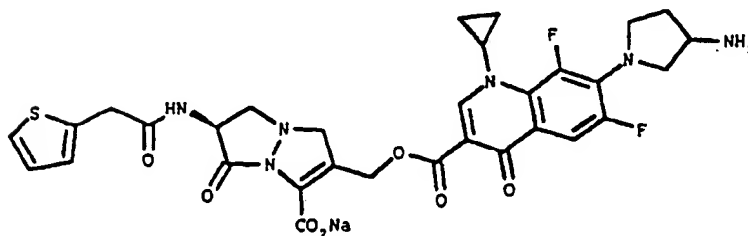


20

25



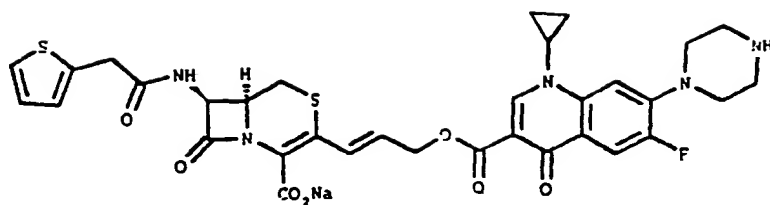
30



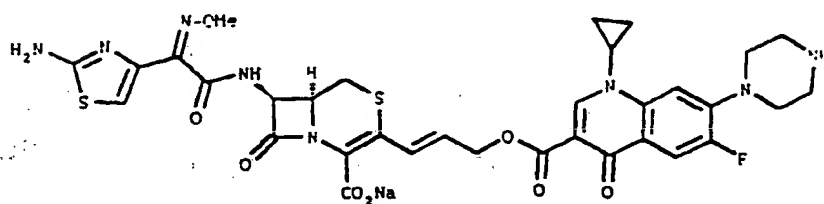
35

-74-

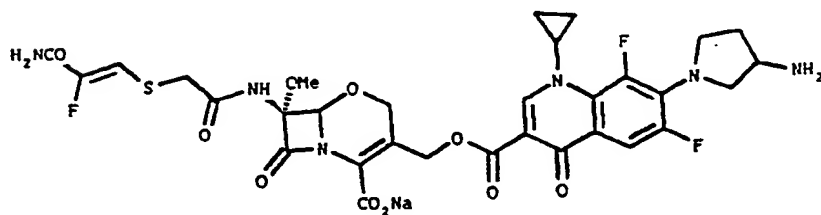
5



10

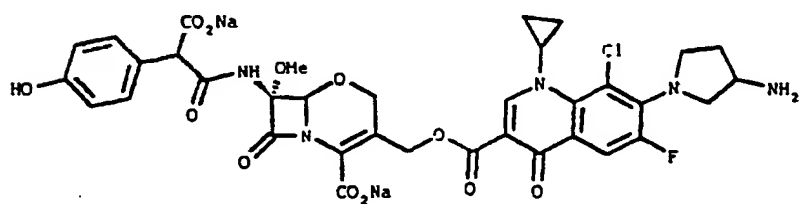


15

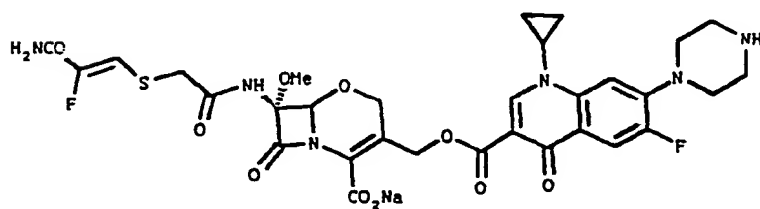


20

25



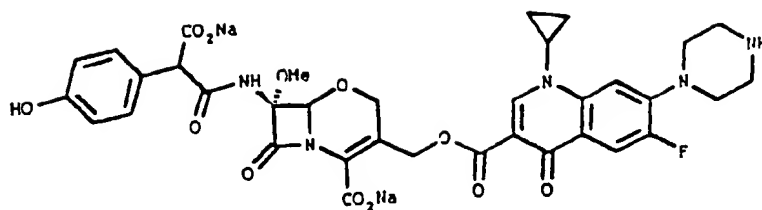
30



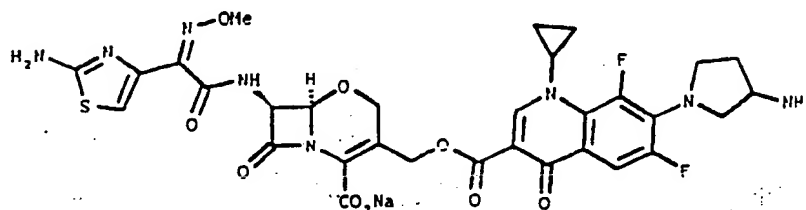
35

-75-

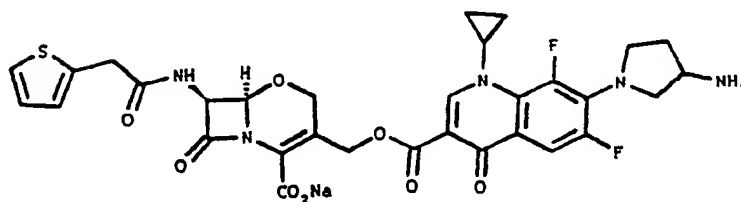
5



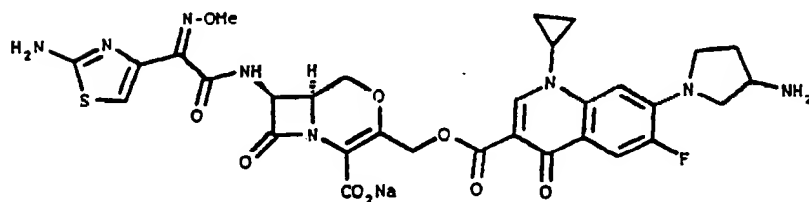
10



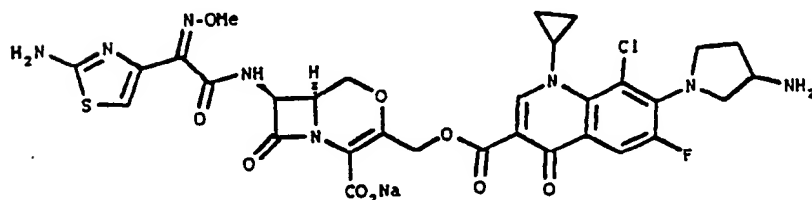
15



20



25

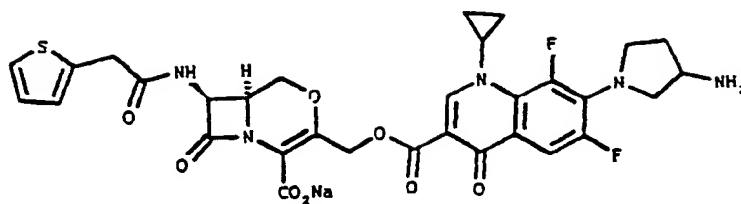


30

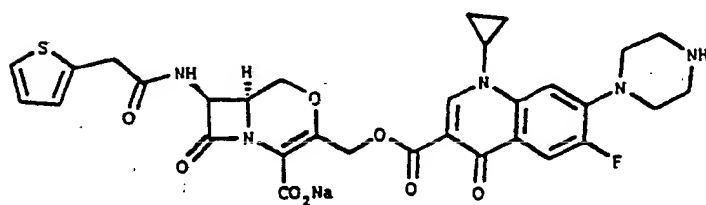
35

-76-

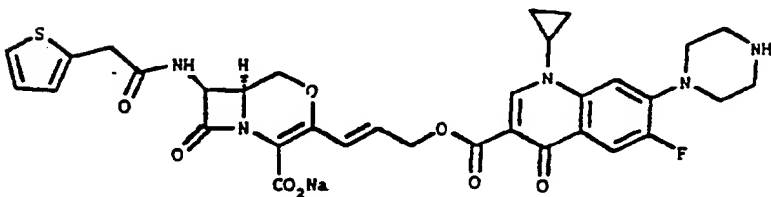
5



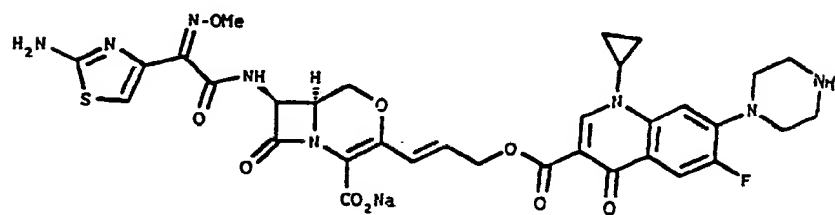
10



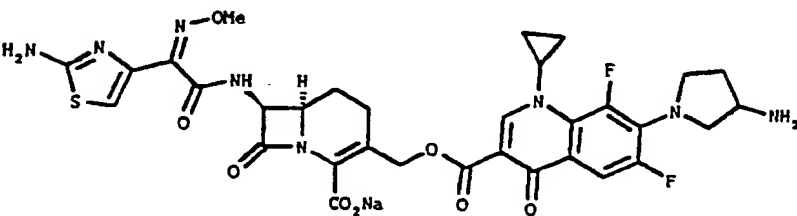
15



20



25

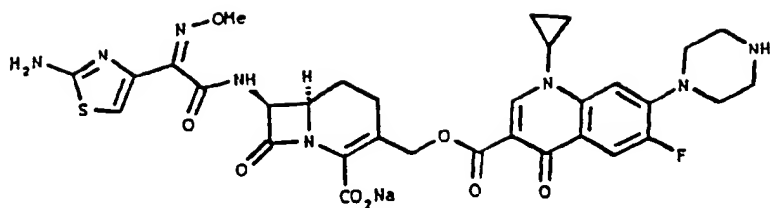


30

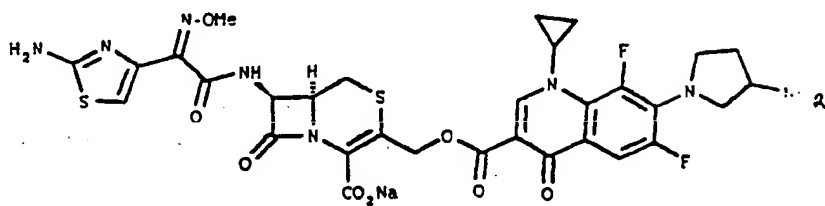
35

-77-

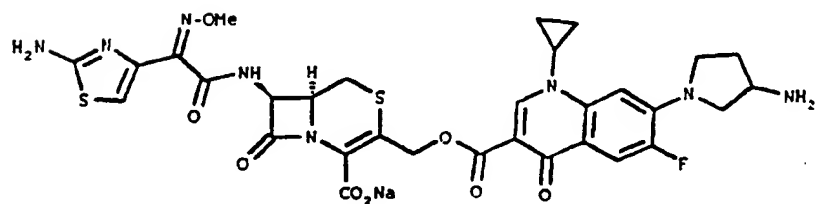
5



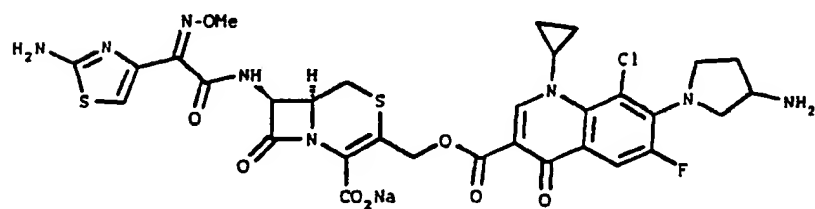
10



15

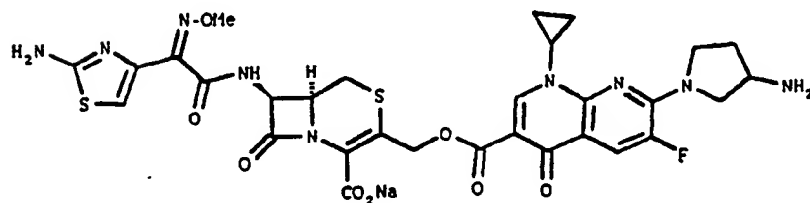


20



25

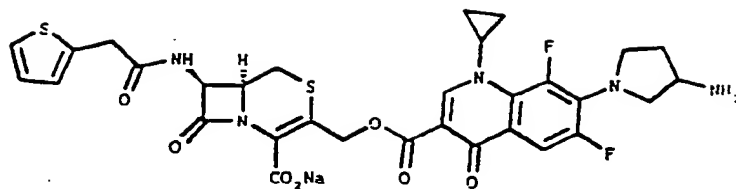
30



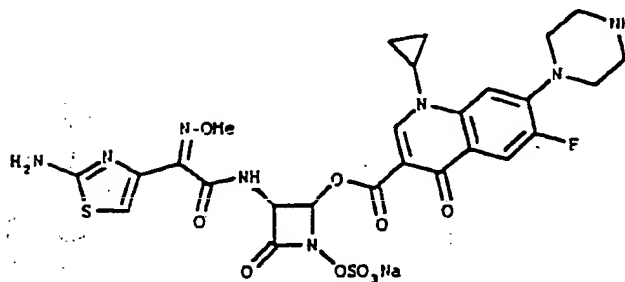
35

-78-

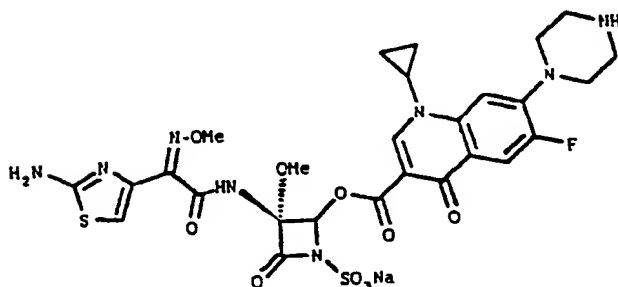
5



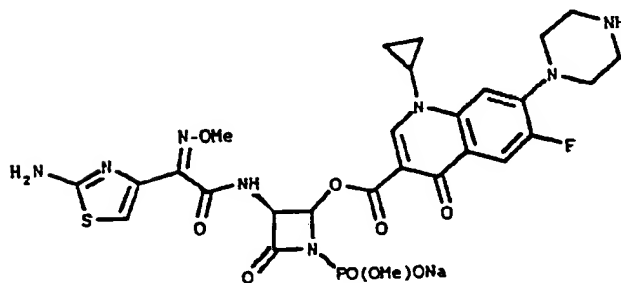
10



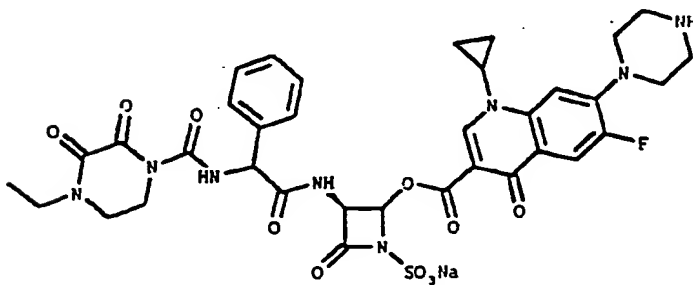
15



20



25

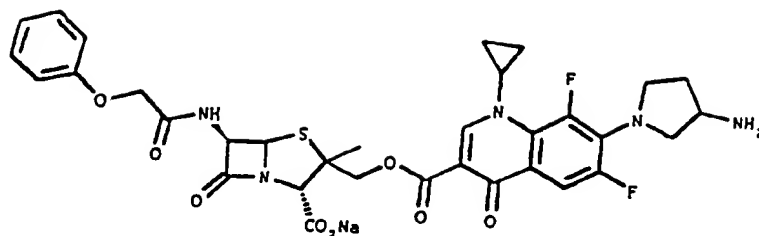


30

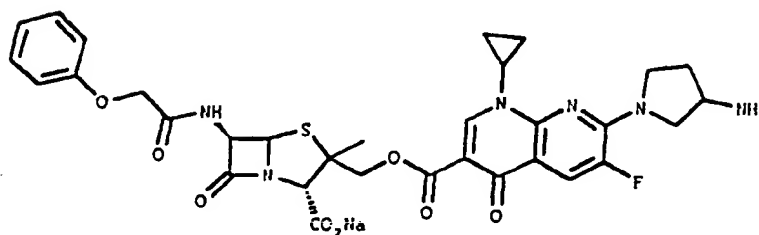
35

-79-

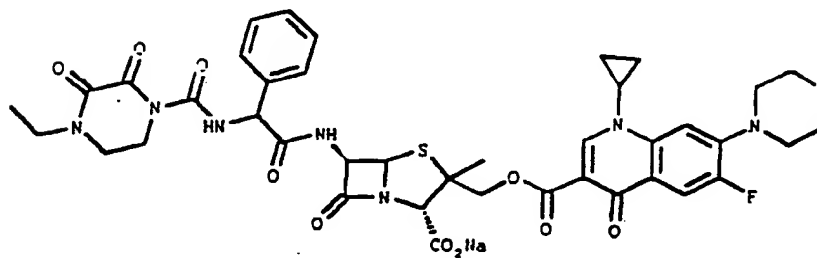
5



10

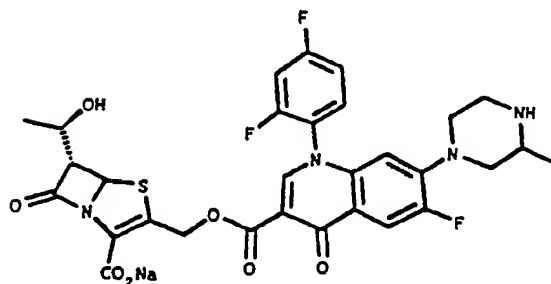


15

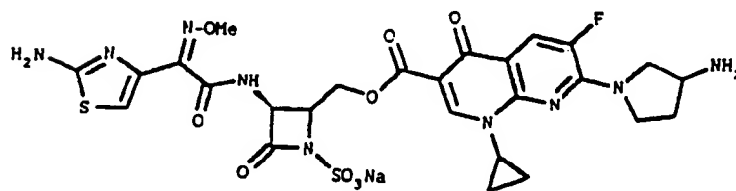


20

25

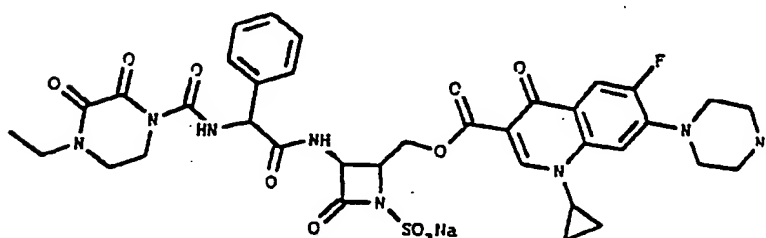
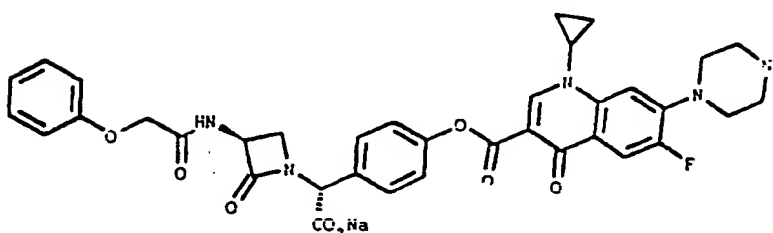
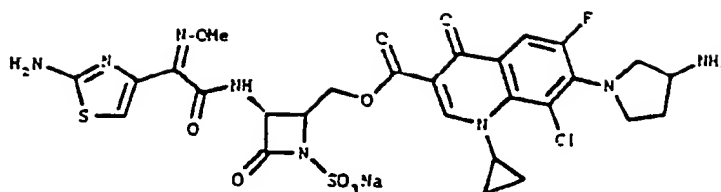


30



35

-80-



Methods of Manufacture

The quinolonyl lactam esters of this invention may be made using any of a variety of synthetic techniques known in the art. Manufacture of quinolonyl lactam esters generally involves the preparation of a lactam-containing moiety, a quinolone moiety and a procedure or set of procedures for linking the lactam-containing and quinolone moieties. Procedures for making a broad variety of lactam-containing moieties and quinolone moieties are well known in the art. For example, procedures for preparing lactam-containing moieties, and related compounds, are described in the following references, all incorporated by reference herein (including articles cited within these references): Cephalosporins and Penicillins: Chemistry and Biology (E. H. Flynn, ed, 1972) Chapters 2, 3, 4, 5, 6, 7, 15 and Appendix I; Recent Advances in the Chemistry of β -Lactam Antibiotics (A.G. Brown and S. M. Roberts, ed., 1985); Topics in Antibiotic Chemistry, Vol. 3, (Part B) and Vol. 4, (P. Sommes,

-81-

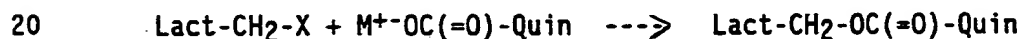
- ed., 1980); Recent Advances in the Chemistry of β -lactam Antibiotics (J. Elks, ed., 1976); Structure-Activity Relationships Among the Semisynthetic Antibiotics (D. Perlman, ed, 1977); Chpts. 1, 2, 3, 4; Antibiotics, Chemotherapeutics and Antibacterial Agents for Disease Control (M. Grayson, ed, 1982); Chemistry and Biology of β -Lactam Antibiotics, Vols 1-3 (K. B. Morin and M. Gorman, eds, 1982); 4 Medicinal Research Reviews 1-24 (1984); 8 Medicinal Research Review 393-440 (1988); 24 Angew. Chem. Int. Ed. Engl. 180-202 (1985); 40 J. Antibiotics 182-189 (1987); European Patent Publication 266,060; 42 J. Antibiotics 993 (1989); U.S. Patent 4,742,053; 35 Chem. Pharm. Bull. 1903-1909 (1987); 32 J. Med. Chem., 601-604 (1989); U.S. Patent 4,791,106; Japanese Patent Publication 62/158291; 31 J. Med. Chem. 1987-1993 (1988); 30 J. Med. Chem., 514-522 (1987); 28 Tet. Let. 285-288 (1987); 28 Tet. Let. 289-292 (1987); 52 J. Org. Chem., 4007-4013 (1987); 40 J. Antibiotics, 370-384 (1987); 40 J. Antibiotics, 1636-1639 (1987); 37 J. Antibiotics, 685-688 (1984); 23 Heterocycles, 2255-2270; 27 Heterocycles, 49-55; 33 Chem. Pharm. Bull. 4371-4381 (1985); 28 Tet. Let., 5103-5106 (1987); 53 J. Org. Chem., 4154-4156 (1988); 39 J. Antibiotics, 1351-1355 (1986); 59 Pure and Appl. Chem., 467-474 (1987); 1987 J.C.S. Chem. Comm.; 44 Tetrahedron, 3231-3240 (1988); 28 Tet. Let., 2883-2886, (1987); 40 J. Antibiotics, 1563-1571 (1987); 33 Chem. Pharm. Bull., 4382-4394 (1985); 37 J. Antibiotics, 57-62 (1984); U.S. Patent 4,631,150; 34 Chem. Pharm. Bull., 999-1014 (1986); 52 J. Org. Chem., 4401-4403 (1987); 39 Tetrahedron, 2505-2513 (1983); 38 J. Antibiotics, 1382-1400 (1985); European Patent Application 053,815; 40 J. Antibiotics, 1563-1571 (1987); 40 J. Antibiotics, 1716-1732 (1987); 47 J. Org. Chem., 5160-5167 (1981); U.S. Patent 4,777,252; U.S. Patent 4,762,922; European Patent Publication 287,734; U.S. Patent 4,762,827; European Patent Publication 282,895; European Patent Publication 282,365; U.S. Patent 4,777,673.

Also, for example, procedures for preparing quinolones useful in the methods of this invention are described in the following references, all incorporated by reference herein

-82-

(including articles listed within these references); 21 Progress in Drug Research, 9-104 (1977); 31 J. Med. Chem., 503-506 (1988); 32 J. Med. Chem., 1313-1318 (1989); 1987 Liebigs Ann. Chem., 871-879 (1987); 14 Drugs Exptl. Clin. Res., 379-383 (1988); 31 J. Med. Chem., 983-991 (1988); 32 J. Med. Chem., 537-542 (1989); 78 J. Pharm. Sci., 585-588 (1989); 26 J. Het. Chem., (1989); 24 J. Het. Chem., 181-185 (1987); U.S. Patent 4,599,334, 35 Chem. Pharm. Bull., 2281-2285 (1987); 29 J. Med. Chem., 2363-2369 (1986); 31 J. Med. Chem., 991-1001 (1988); 25 J. Het. Chem., 479-485 (1988); European Patent Publication 266,576; European Patent Publication 251,308, 36 Chem. Pharm. Bull., 1223-1228 (1988); European Patent Publication 227,088; European Patent Publication 227,039; European Patent Publication 228,661; 31 J. Med. Chem., 1586-1590 (1988); 31 J. Med. Chem., 1598-1611 (1988); and 23 J. Med. Chem., 1358-1363 (1980).

The quinolonyl lactam esters of this invention may be made by the following general reaction sequence:



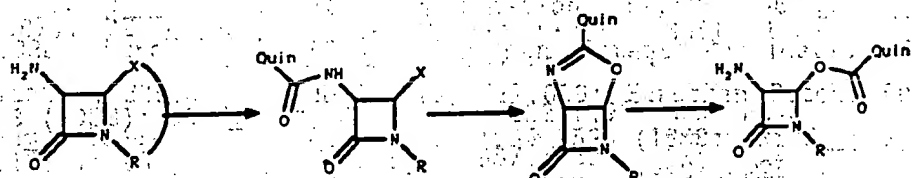
where X is a reactive leaving group (such as halo, a sulfonate ester or other activated hydroxyl functionality), "Lact" generically represents an appropriately protected lactam-containing moiety (such as a penem, carbapenem, oxacephem, or carbacephem) and "Quin" represents an appropriately protected quinolone moiety. The reaction can be envisioned as a nucleophilic displacement of the reactive X substituent from the lactam by the quinolone carboxylic acid or salt, to form an ester coupled conjugate of the lactam and quinolone.

For Lact and Quin, certain functional groups contained in the structures (such as carboxyl, hydroxyl, and amino) may need to be blocked in order to prevent undesired competing side reactions from occurring with X. For example, suitable protecting groups for carboxyl substituents include esters;

-83-

protecting groups for hydroxyl substituents include ethers, esters, and carbonates; and protecting groups for amino substituents include carbamates and amides. If such protecting groups are employed, then appropriate deprotecting chemistry, that will not decompose the ester coupled conjugate, may be required to obtain antimicrobially-active products.

If the lactam-containing moiety is a monocyclic beta-lactam, an alternative coupling strategy may be employed as outlined by the following sequence, where X is a heteroatom (O, S, halo, etc.) substituent linked to the lactam.



This sequence involves amide formation between the lactam and the quinolone, rearrangement displacing X and liberation of the ester by hydrolysis. The lactam containing structure may initially be mono- or bicyclic. The ester coupled product will be monocyclic.

Compositions

The compositions of this invention comprise:

- (a) a safe and effective amount of a quinolonyl lactam ester; and
- (b) a pharmaceutically-acceptable carrier.

A "safe and effective amount" of a quinolonyl lactam ester is an amount that is effective, to inhibit microbial growth at the site of an infection to be treated in a human or lower animal subject, without undue adverse side effects (such as toxicity, irritation, or allergic response), commensurate with a reasonable benefit/risk ratio when used in the manner of this invention. The specific "safe and effective amount" will, obviously, vary with such factors as the particular condition being treated, the physical condition of the patient, the duration of treatment, the nature of concurrent therapy (if any), the specific dosage form

-84-

to be used, the carrier employed, the solubility of the quinolonyl lactam esters therein, and the dosage regimen desired for the composition.

5 The compositions of this invention are preferably provided in unit dosage form. As used herein, a "unit dosage form" is a composition of this invention containing an amount of a quinolonyl lactam ester that is suitable for administration to a human or lower animal subject, in a single dose, according to good medical practice. These compositions preferably contain
10 from about 30 mg to about 20,000 mg, more preferably from about 50 mg (milligrams) to about 7000 mg, more preferably from about 500 mg to about 1500 mg, of a quinolonyl lactam ester.

The compositions of this invention may be in any of a variety of forms, suitable (for example) for oral, rectal,
15 topical or parenteral administration. Depending upon the particular route of administration desired, a variety of pharmaceutically-acceptable carriers well-known in the art may be used. These include solid or liquid fillers, diluents, hydrotropes, surface-active agents, and encapsulating substances.
20 Optional pharmaceutically-active materials may be included, which do not substantially interfere with the antimicrobial activity of the quinolonyl lactam ester. The amount of carrier employed in conjunction with the quinolonyl lactam ester is sufficient to provide a practical quantity of material for administration per
25 unit dose of the quinolonyl lactam ester. Techniques and compositions for making dosage forms useful in the methods of this invention are described in the following references, all incorporated by reference herein: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, editors, 1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel,
30 Introduction to Pharmaceutical Dosage Forms 2d Edition (1976).

In particular, pharmaceutically-acceptable carriers for systemic administration include sugars, starches, cellulose and its derivatives, malt, gelatin, talc, calcium sulfate, vegetable
35 oils, synthetic oils, polyols, alginic acid, phosphate buffer solutions, emulsifiers, isotonic saline, and pyrogen-free water.

-85-

Preferred carriers for parenteral administration include propylene glycol, ethyl oleate, pyrrolidone, ethanol, and sesame oil. Preferably, the pharmaceutically-acceptable carrier, in compositions for parenteral administration, comprises at least about 90% by weight by the total composition.

Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. These oral forms comprise a safe and effective amount, usually at least about 5%, and preferably from about 25% to about 50%, of the quinolonyl lactam ester. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules, and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents and flavoring agents. Preferred carriers for oral administration include gelatin, propylene glycol, cottonseed oil and sesame oil.

The compositions of this invention can also be administered topically to a subject, i.e., by the direct laying on or spreading of the composition on the epidermal or epithelial tissue of the subject. Such compositions include, for example, lotions, creams, solutions, gels and solids. These topical compositions preferably comprise a safe and effective amount, usually at least about 0.1%, and preferably from about 1% to about 5%, of the quinolonyl lactam ester. Suitable carriers for topical administration preferably remain in place on the skin as a continuous film, and resist being removed by perspiration or immersion in water. Generally, the carrier is organic in nature and capable of having dispersed or dissolved therein the quinolonyl lactam ester. The carrier may include

-86-

pharmaceutically-acceptable emollients, emulsifiers, thickening agents, and solvents.

Methods of Administration

5 This invention also provides methods of treating or preventing an infectious disorder in a human or other animal subject, by administering a safe and effective amount of a quinolonyl lactam ester to said subject. As used herein, an "infectious disorder" is any disorder characterized by the presence of a microbial infection. Preferred methods of this invention are for the treatment of bacterial infections. Such infectious disorders include (for example) central nervous system infections, external ear infections, infections of the middle ear (such as acute otitis media), infections of the cranial sinuses, eye infections, infections of the oral cavity (such as infections of the teeth, gums and mucosa), upper respiratory tract infections, lower respiratory tract infections, genitourinary infections, gastrointestinal infections, gynecological infections, septicemia, bone and joint infections, skin and skin structure infections, bacterial endocarditis, burns, antibacterial prophylaxis of surgery, and antibacterial prophylaxis in immunosuppressed patients (such as patients receiving cancer chemotherapy, or organ transplant patients).

20 The quinolonyl lactam esters and compositions of this invention can be administered topically or systemically. Systemic application includes any method of introducing the quinolonyl lactam ester into the tissues of the body, e.g., intrathecal, epidural, intramuscular, transdermal, intravenous, intraperitoneal, subcutaneous, sublingual, rectal, and oral administration. The specific dosage of antimicrobial to be administered, as well as the duration of treatment, are mutually dependent. The dosage and treatment regimen will also depend upon such factors as the specific quinolonyl lactam ester used, the resistance pattern of the infecting organism to the quinolonyl lactam ester used, the ability of the quinolonyl lactam ester to reach minimum inhibitory concentrations at the site of the infection, the nature and extent of other infections

-87-

(if any), the personal attributes of the subject (such as weight), compliance with the treatment regimen, and the presence and severity of any side effects of the treatment.

Typically, for a human adult (weighing approximately 70 kilograms), from about 75 mg to about 30,000 mg, more preferably from about 100 mg to about 20,000 mg, more preferably from about 500 mg to about 3500 mg, of quinolonyl lactam ester are administered per day. Treatment regimens preferably extend from about 1 to about 56 days, more preferably from about 7 to about 28 days, in duration. Prophylactic regimens (such as avoidance of opportunistic infections in immunocompromised patients) may extend 6 months, or longer, according to good medical practice.

A preferred method of parenteral administration is through intramuscular injection. As is known and practiced in the art, all formulations for parenteral administration must be sterile. For mammals, especially humans, (assuming an approximate body weight of 70 kilograms) individual doses of from about 100 mg to about 7000 mg, preferably from about 500 mg to about 1500 mg, are acceptable.

A preferred method of systemic administration is oral. Individual doses of from about 100 mg to about 2500 mg, preferably from about 250 mg to about 1000 mg are preferred.

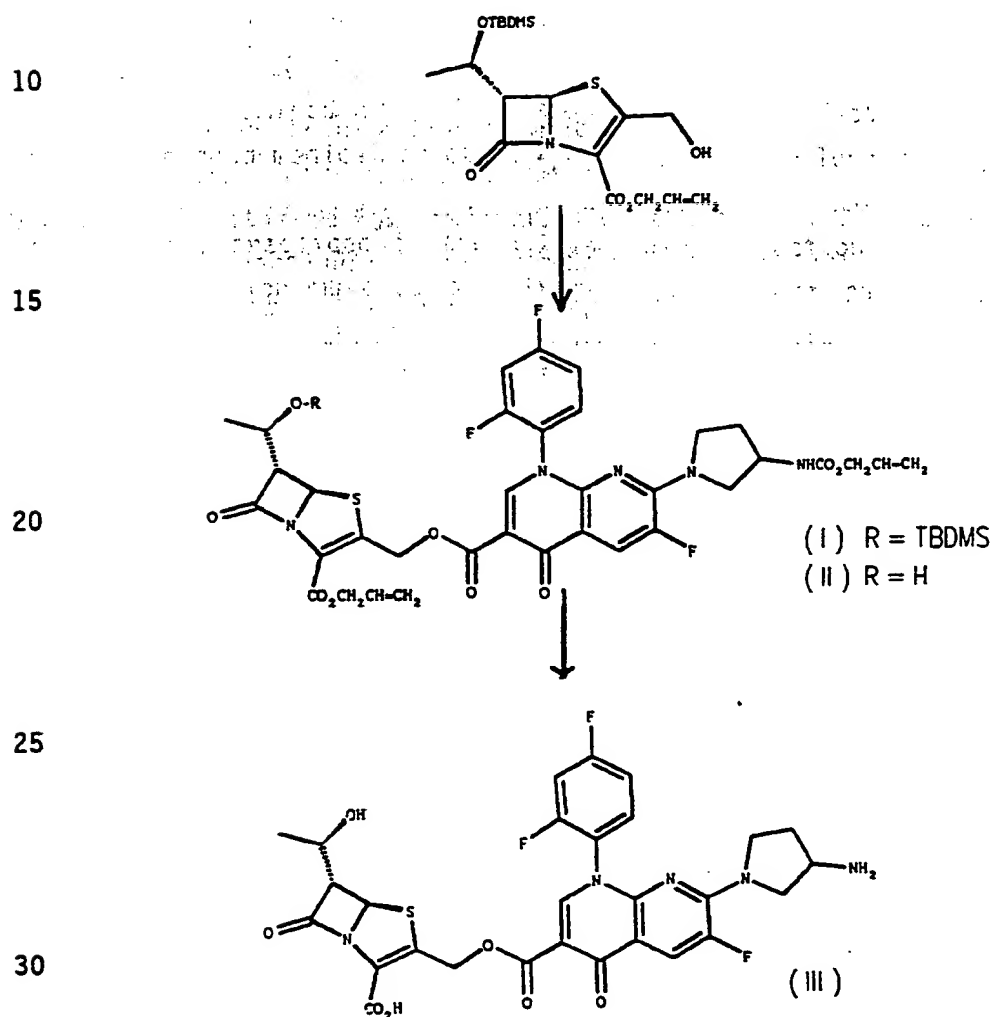
Topical administration can be used to deliver the quinolonyl lactam ester systemically, or to treat a local infection. The amounts of quinolonyl lactam ester to be topically administered depends upon such factors as skin sensitivity, type and location of the tissue to be treated, the composition and carrier (if any) to be administered, the particular quinolonyl lactam ester to be administered, as well as the particular disorder to be treated and the extent to which systemic (as distinguished from local) effects are desired.

The following non-limiting examples illustrate the compounds, compositions, processes, and uses of the present invention.

-88-

EXAMPLE 1

[5R][5 α ,6 α]-3-[[7-[(3-amino-1-pyrrolidinyl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-3-(1,8-naphthyridinyl)] carbonyloxy]methyl]-6-(1(R)-hydroxyethyl)-7-oxo-4-thia-1-aza-bicyclo[3.2.0]hept-2-ene-2-carboxylic acid, according to this invention is made by the following general reaction sequence.



-89-

Approximately 0.28 mmol (0.112 g) of [5R][5 α ,6 α]]-3-hydroxymethyl-6-(1(R)-t-butyl dimethylsiloxyethyl)-7-oxo-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, allyl ester (made according to U.S. Patent 4,631,150, Battistini et al., issued December 23, 1986, incorporated by reference herein) is dissolved in approximately 10 ml THF (tetrahydrofuran). Under a nitrogen blanket, at approximately 22°C (72°F), approximately 0.32 mmol of diethylazodicarboxylate, 0.32 mmol of 6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-7-[3-[3-(1-propenyl)oxycarbonyl]amino-1-pyrrolidinyl]-3-(1,8-naphthyridine)-carboxylic acid and 0.32 mmol PPh₃ (triphenyl phosphine) are sequentially added with stirring. After approximately 15 minutes, 10 ml phosphate buffer (0.5 M, pH 7.0) is added, the THF is rapidly evaporated, and the aqueous residue is extracted with dichloromethane. Drying and removal of the solvent in vacuo yields the crude Product (I), which is further purified by flash chromatography.

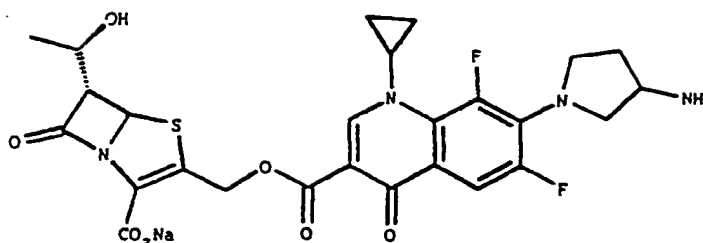
Approximately 0.15 g of Product (I) (0.18 mmol) is dissolved in 20 ml THF. Then 40 microliters of glacial acetic acid and 60 mg of tetrabutyl ammonium fluoride are added and the reaction is allowed to stand approximately 24 hours at ambient temperature. The THF is evaporated and the residue is taken up in dichloromethane. Extraction with aqueous bicarbonate, and solvent reduction, yields product (II).

Approximately 60 mg of Product (II) (0.08 mmol) is then dissolved in 15 ml THF at ambient temperature, and 5 mg PPh₃, 44 mg sodium ethylhexanoate and 5 mg Pd(PPh₃)₄ are added with stirring. Within several minutes a precipitate forms and is collected by filtration. The solid final product (III) is purified to analytical purity by repeated trituration.

Similarly, the following quinolonyl lactam esters are prepared according to the general procedure of this Example, with substantially similar results.

-90-

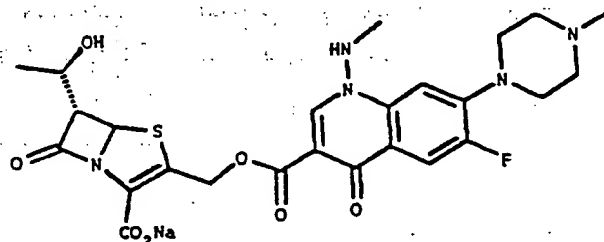
5



using the quinolone 7-(3-aminopyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (prepared according to J. P. Sanchez, et al., J. Med. Chem., 1988, 31, 983)

10

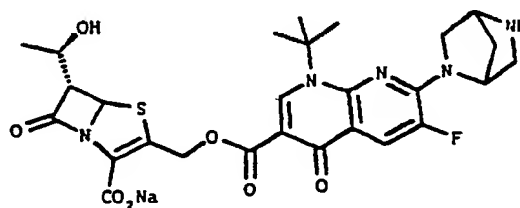
15



20

using the quinolone 6-fluoro-1,4-dihydro-1-methylamino-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinoline carboxylic acid (prepared according to M.P. Wentland, et al., J. Med. Chem. 1984, 27, 1103)

25



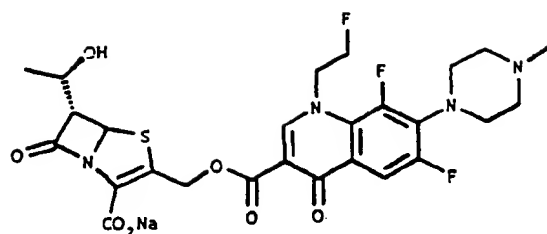
30

using the naphthyridinone 7-(2,5-diazabicyclo[2.2.1]heptan-2-yl)-1-(1,1-dimethylethyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (prepared according to A. Weber, et al., Eur. Pat. Appl. EP 266576)

35

-91-

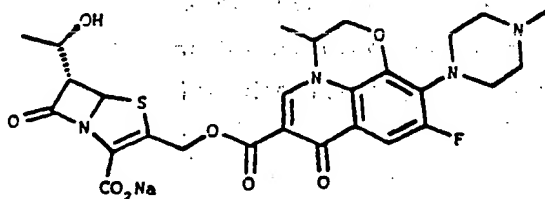
5



10

using the quinolone 6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxo-7-(4-methyl-1-piperazinyl)-3-quinolinecarboxylic acid (prepared according to T. Iridura, Aust. Pat. Specif. AU 537813)

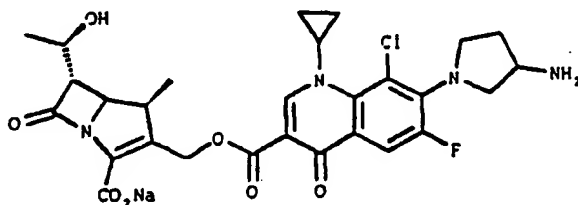
15



20

using the quinolone 9-fluoro-4,7-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid (prepared according to I. Hagakawa et al., Chem. Pharm Bull. 1984, 32, 4907)

25



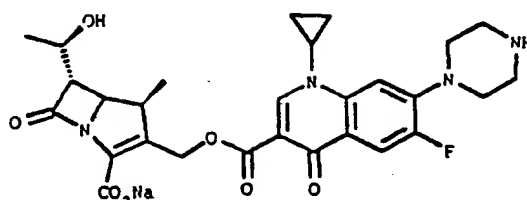
30

35

using the quinolone 7-(3-aminopyrrolidinyl)-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (prepared according to J. P. Sanchez, et al., J. Med. Chem., 1988, 31, 983) and the 8-lactam [5R-[4 β ,5 α ,6 α]]-6-[(R)-1-(t-butyl dimethylsilyloxy)ethyl]-2-(hydroxymethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid allyl ester

-92-

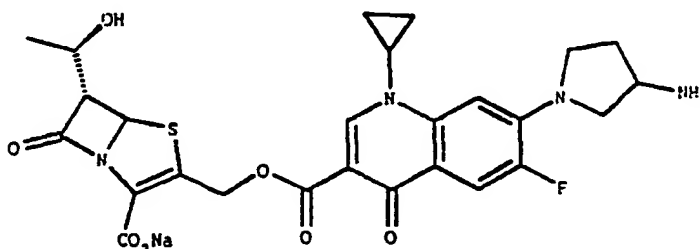
(prepared according to B.G. Christensen et al., Eur. Pat. Appl. EP 185315 A1, 1986)



using the quinolone 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-((1-piperazinyl)-3-quinolinecarboxylic acid (prepared according to K. Grohe et al., Ger. Offen. DE 3142854) and the B-lactam [5R-[4 β ,5 α ,6 α]]-6-[(R)-1-(t-butyl dimethylsilyloxy)ethyl]-2-(hydroxymethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid allyl ester (prepared according to B.G. Christensen et al., Eur. Pat. Appl. EP 185315 A1, 1986).

EXAMPLE 2

According to the general procedure of Example 1, the following quinolonyl lactam ester is made:

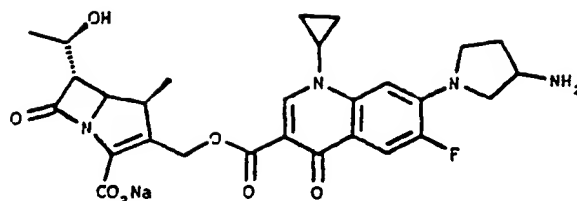


using the quinolone 7-(3-aminopyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (prepared according to J. P. Sanchez, et al., J. Med. Chem., 1988, 31, 983).

Similarly, the following quinolonyl lactam ester is prepared according to the general procedure of this Example, with substantially similar results.

-93-

5



10

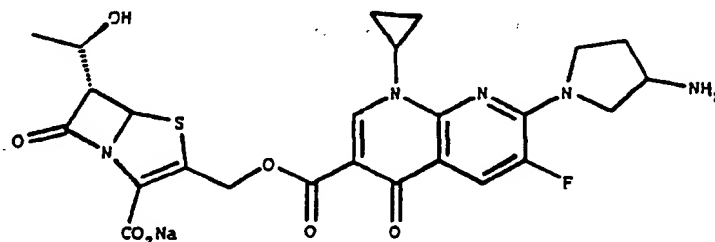
using the 8-lactam [5R-[4 β ,5 α ,6 α]]-6-[(R)-1-(t-butyltrimethylsilyloxy)ethyl]-2-(hydroxymethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid allyl ester (prepared according to B.G. Christensen et al., Eur. Pat. Appl. EP 185315 A1, 1986).

EXAMPLE 3

15

According to the general procedure of Example 1, the following quinolonyl lactam ester is made:

20



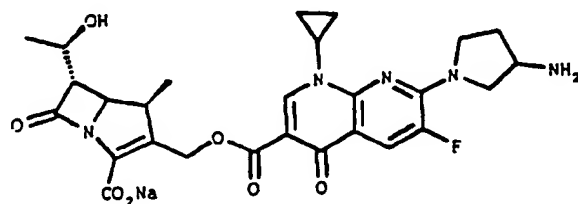
25

using the naphthyridinone 7-(3-aminopyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (prepared according to J. P. Sanchez, et al., J. Med. Chem., 1988, 31, 983).

30

Similarly, the following quinolonyl lactam ester is prepared according to the general procedure of this Example, with substantially similar results.

35

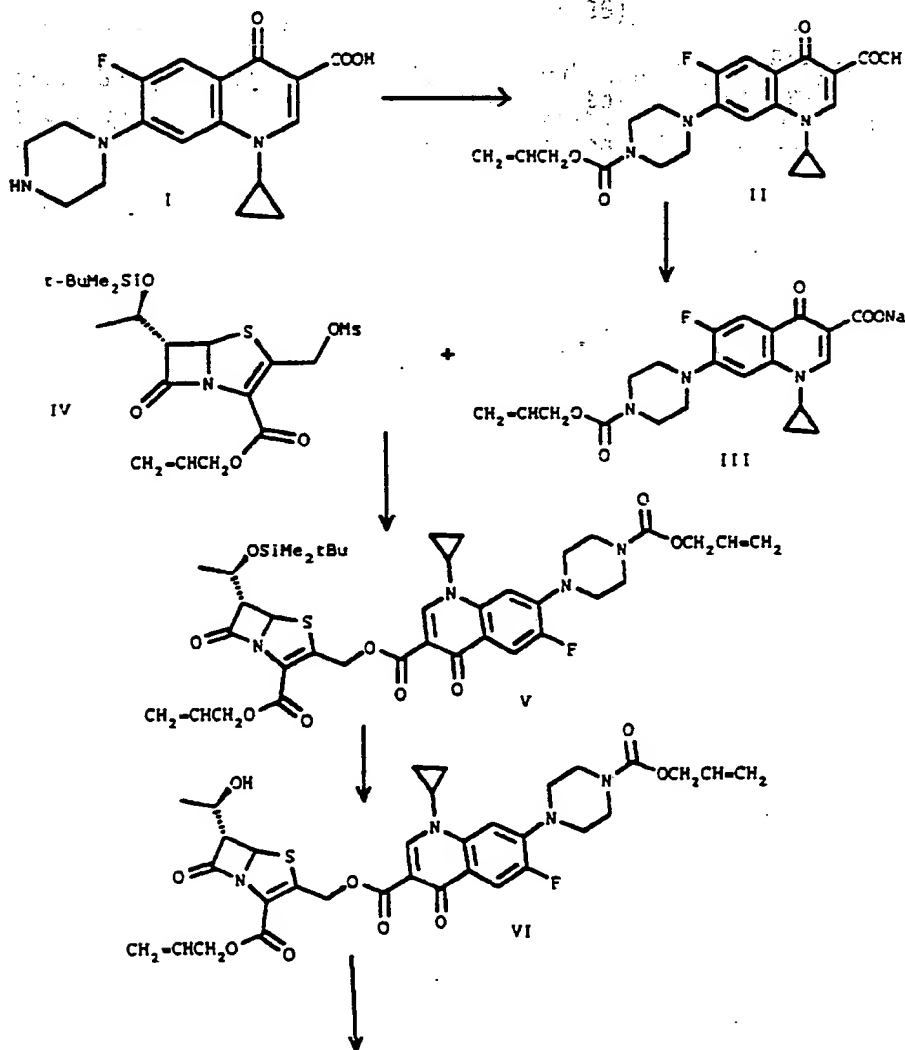


-94-

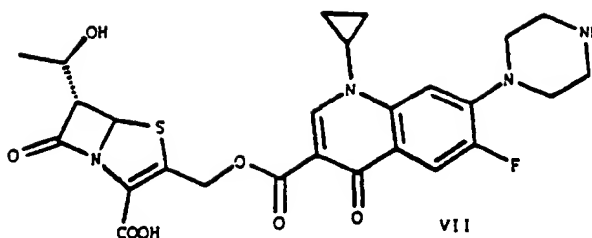
using the 8-lactam [5R-[4 β ,5 α ,6 α]]-6-[(R)-1-(*t*-butyldimethylsilyloxy)ethyl]-2-(hydroxymethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid allyl ester (prepared according to B.G. Christensen et al., Eur. Pat. Appl. EP 185315 A1, 1986)

EXAMPLE 4

[5R-[5 α ,6 α]]-3-[[[1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoliny]carbonyloxy]methyl]-6-[(R)-1-hydroxyethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic Acid



-95-



5
10
15
20
25

A mixture of approximately 5.0 g of ciprofloxacin I in 175 ml of water at approximately 0°C is adjusted to approximately pH 12 by adding 1N NaOH. To this solution is added approximately 44 ml of acetone followed by the dropwise addition of approximately 2.7 g of allylchloroformate in 33 ml of acetone. The reaction is stirred approximately one hour in the cold while maintaining the mixture at pH 10-12 by addition of more 1N NaOH. Then the reaction is concentrated to approximately 125 ml and is extracted twice with ether. The aqueous layer is cooled in an ice bath, acidified with 10% HCl and is extracted three times with ethyl acetate. The extract is washed with water, dried over Na₂SO₄, filtered, and the filtrate is concentrated to dryness to give II. To a solution of approximately 6 g of II in CH₂Cl₂ at approximately 0°C is added dropwise a solution of approximately 0.73 g of NaOH in 5 ml of methanol. The mixture is stirred for one hour at ambient temperature, and concentrated to dryness. The residue is triturated in ether and the sodium salt III is collected by filtration.

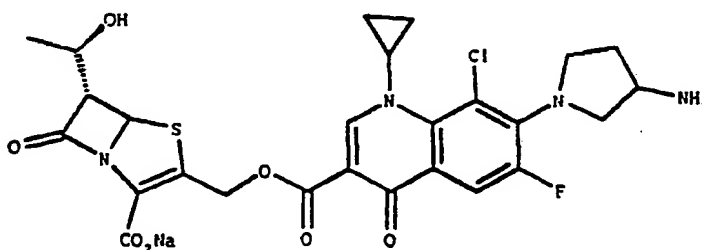
30
35

Separately, to a solution of approximately 5.0 g of [5R-[5 α ,6 β]]-3-hydroxymethyl-6-(1-(R)-t-butylidimethylsiloxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid allyl ester and 1.7 ml of triethylamine in 30 ml of CH₂Cl₂ at approximately -40°C is added approximately 1.1 ml of mesyl chloride. The reaction is stirred for approximately 10 minutes, then washed with 10% aqueous NaHCO₃ and water. The organic phase is dried over Na₂SO₄, filtered, and the filtrate is concentrated to dryness to give IV. To a solution of approximately 4.3 g of the mesylate IV in 30 ml of DMF at approximately 0°C is added

-96-

approximately 3.9 g of III and the reaction is stirred cold for approximately four hours and at ambient temperature for approximately one hour. The reaction is concentrated to dryness in vacuo and the residue is dissolved in CH_2Cl_2 and washed with water. The organic phase is dried over Na_2SO_4 , filtered and the filtrate is concentrated to dryness. The residue is purified by flash chromatography (silica gel) to give V. To a mixture of approximately 2.6 g of V and 2 ml of glacial acetic acid in 30 ml of THF at room temperature is added approximately 3.5 g of tetra-n-butylammonium fluoride trihydrate. The mixture is stirred for approximately 30 hours, then concentrated to dryness and residue is purified by flash chromatography (silica gel) to give VI. To a mixture of approximately 1.3 g of VI, 0.19 ml of water and 0.027 g of bis(triphenylphosphine)palladium chloride in approximately 36 ml of CH_2Cl_2 at approximately 19°C is added approximately 1.1 ml of tributyltinhydride. The mixture is rapidly stirred for approximately 10 minutes and the precipitate is collected by filtration. The solid is triturated in acetone and is collected by filtration to afford the title compound VII.

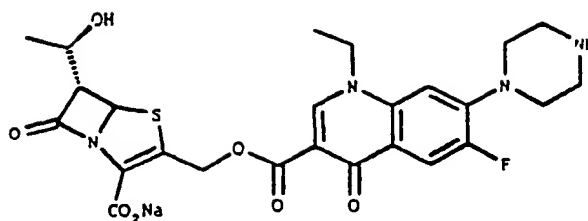
Similarly, the following quinolonyl lactam esters are prepared according to the general procedure of this Example, with substantially similar results.



using the quinolone 7-(3-aminopyrrolidiny)-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (prepared according to J. P. Sanchez, et al., J. Med. Chem., 1988, 31, 983)

-97-

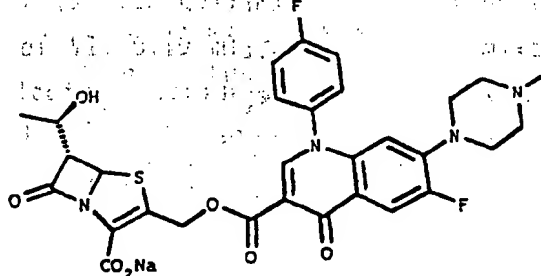
5



10

using the quinolone 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid (prepared according to H. Koga, et al., J. Med. Chem., 1980, 23, 1358)

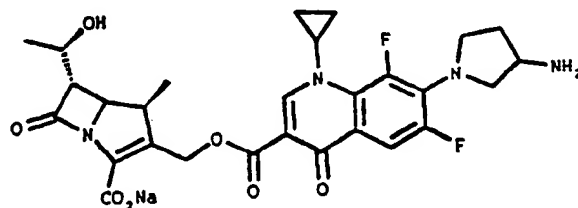
15



20

using the quinolone 6-fluoro-1-(4-fluorophenyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl) 4-oxo-3-quinolinecarboxylic acid (prepared according to D.T.W. Chu et al., J. Med. Chem. 1985, 28, 1558)

25



30

35

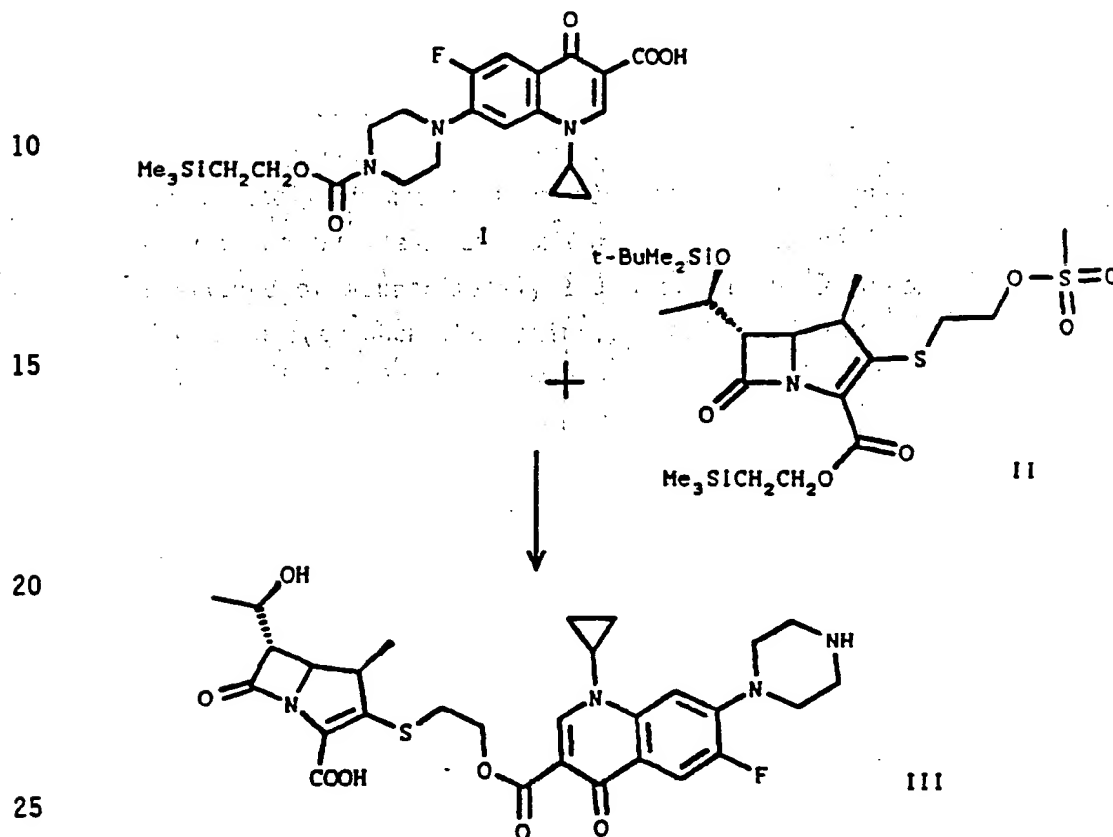
using the quinolone 7-(3-aminopyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (prepared according to J. P. Sanchez, et al., J. Med. Chem., 1988, 31, 983) and the B-lactam [5R-[4 β ,5 α ,6 α]]-6-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-2-(hydroxymethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0]

-98-

hept-2-ene-2-carboxylic acid allyl ester (prepared according to B.G. Christensen et al., Eur. Pat. Appl. EP 185315 A1, 1986).

EXAMPLE 5

Product III, according to this invention, is made by the following general reaction sequence.



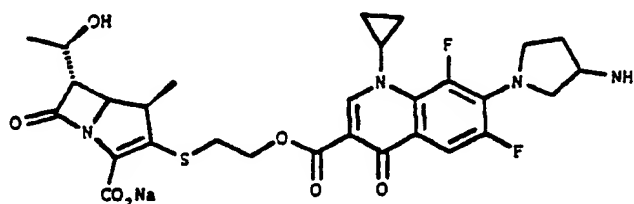
Approximately 1.26 g of ciprofloxacin and 1.59 g NaHCO_3 is suspended in approximately 25 ml of water and stirred for approximately 1 hour. Approximately 0.72 g of 2-(trimethylsilyl) ethyl chloroformate (made according to 38 *Zhur obschei Khim.* 1179 (1968)) in approximately 10 ml of tetrahydrofuran is added dropwise to the stirring aqueous solution. After approximately 1 hour the mixture is poured into 150 ml of chloroform and acidified with 150 ml of cold 0.1M HCl. The aqueous phase is extracted with chloroform again and the combined chloroform

-99-

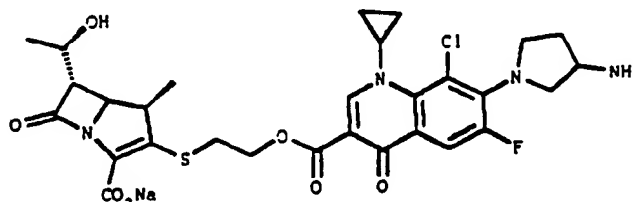
layers are washed successively with cold 0.1M HCl, water, and saturated aqueous sodium chloride. The chloroform solution is dried over Na₂SO₄, filtered, and concentrated. The residue is triturated with ether to provide product I after filtration.

5 A mixture of approximately 0.16 g of product I, 0.20 g of product II (prepared as above), and 0.040 g of NaHCO₃ are combined in approximately 1 ml of dimethylformamide under an inert atmosphere. The mixture is heated at approximately 70°C for 8 hours and then cooled to room temperature. The addition of approximately 0.50 g of tetra-n-butylammonium fluoride trihydrate is followed by stirring for approximately 16 hours at room temperature. The mixture is then eluted through a DowexR 50x4 (Na cycle) column with deionized water. The appropriate fractions are partially concentrated in vacuo, then lyophilized to give the final product III.

15 Similarly, the following quinolonyl lactam esters are prepared according to the general procedure of this Example, with substantially similar results.

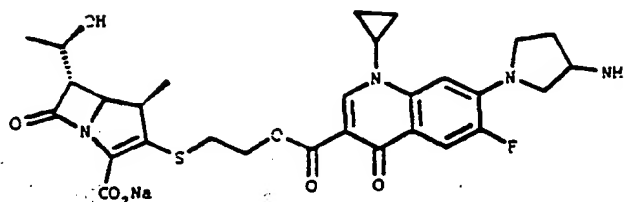


using the quinolone 7-(3-aminopyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (prepared according to J. P. Sanchez, et al., J. Med. Chem., 1988, 31, 983)

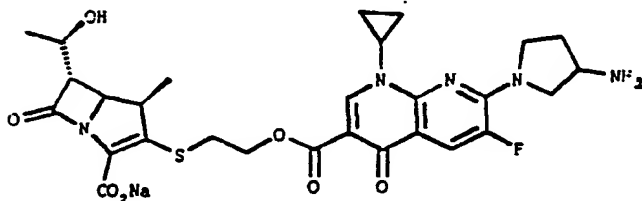


-100-

using the quinolone 7-(3-aminopyrrolidinyl)-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro -4-oxo-3-quinolinecarboxylic acid (prepared according to J. P. Sanchez, et al., J. Med. Chem., 1988, 31, 983)



using the quinolone 7-(3-aminopyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro -4-oxo-3-quinolinecarboxylic acid (prepared according to J. P. Sanchez, et al., J. Med. Chem., 1988, 31, 983)

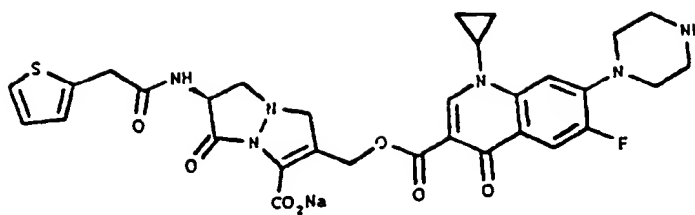


using the naphthyridinone 7-(3-aminopyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro -4-oxo-1,8-naphthyridine-3-carboxylic acid (prepared according to J. P. Sanchez, et al., J. Med. Chem., 1988, 31, 983).

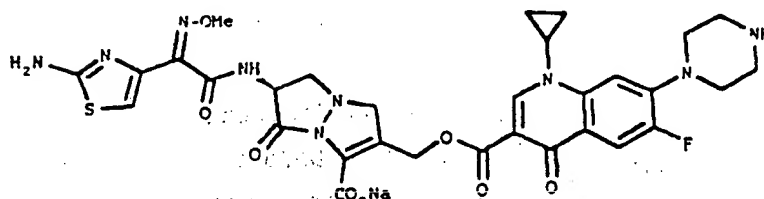
The following other quinolonyl lactam esters are made by the general procedures of this Example and Examples 1 - 4, with substantially similar results.

- 101 -

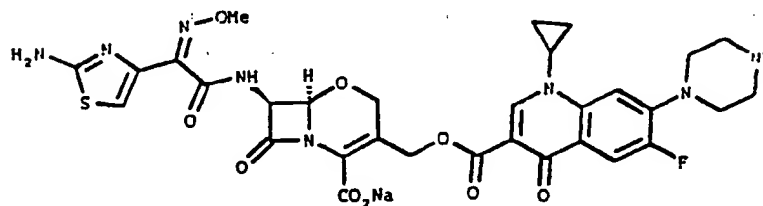
5



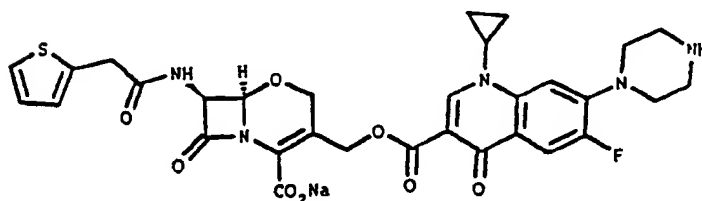
10



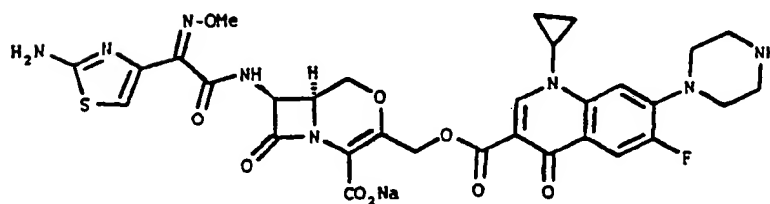
15



20



25

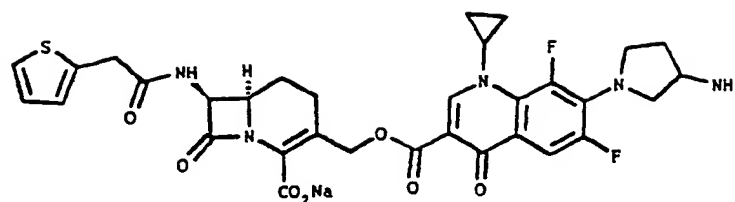


30

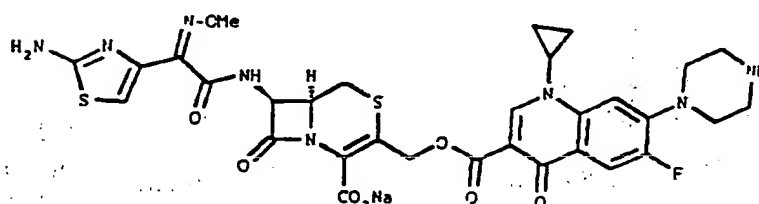
35

-102-

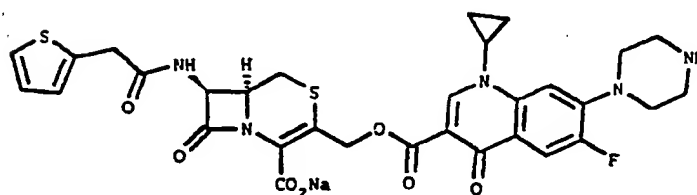
5



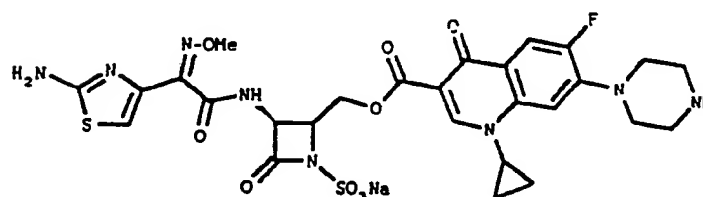
10



15

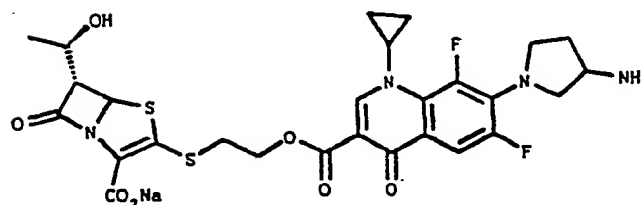


20



25

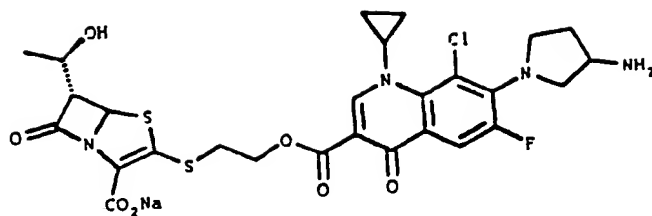
30



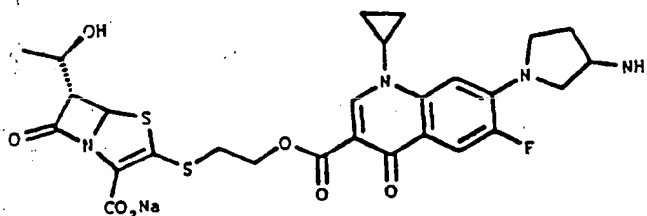
35

-103-

5

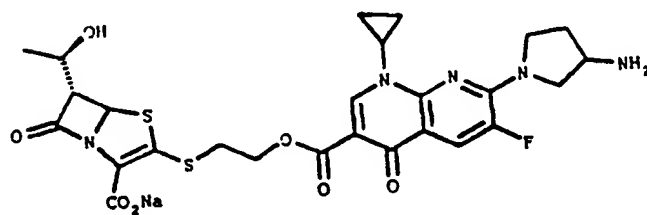


10

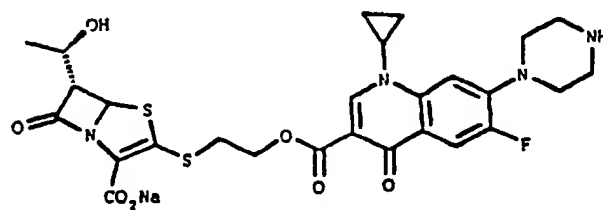


15

20



25



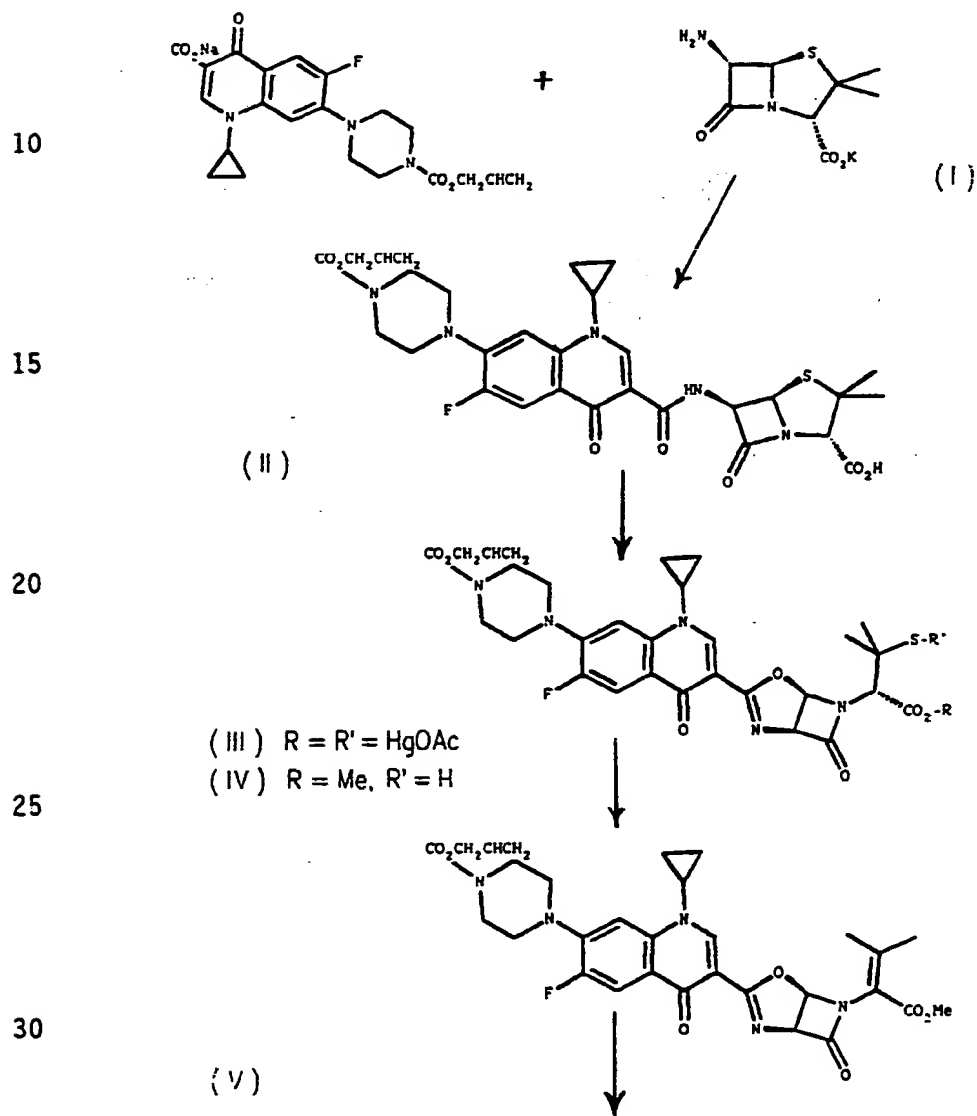
30

35

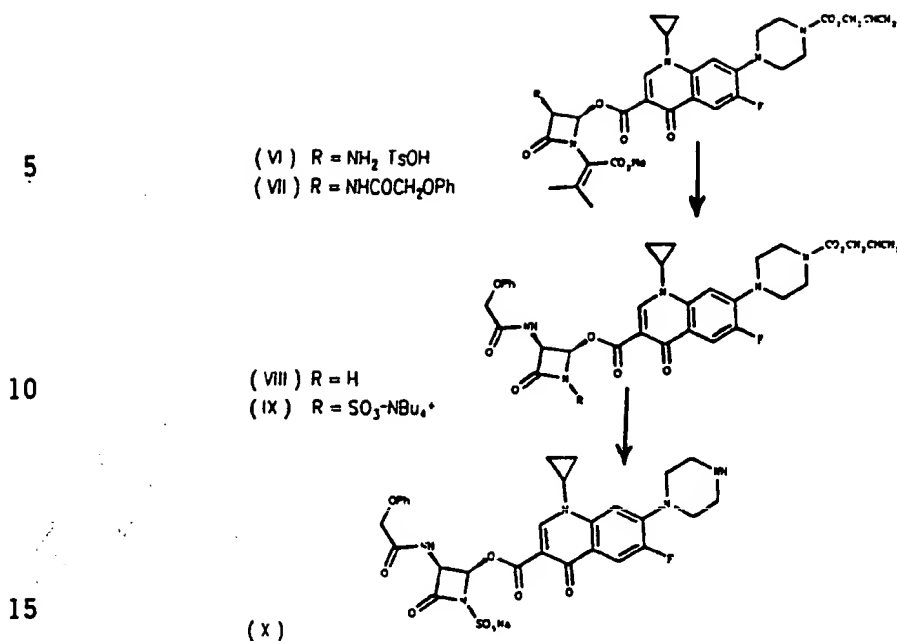
-104-

EXAMPLE 6

[3S-(2b,3b)]-2-[[1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoliny]carbonyloxy]-3-[(phenoxyacetyl)amino]-4-oxo-1-azetidinesulfonic acid sodium salt, according to this invention, is made by the following general reaction sequence.



-105-



An anhydrous solution of approximately 20 g 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-[4-[2-propenyloxy)carbonyl]-1-piperazinyl]-3-quinolinecarboxylic acid sodium salt and 6.4 ml of triethylamine in 100 ml of dioxane and 20 ml of acetone is cooled to 0°C (32°F). To this stirred solution is added 4.4 ml of ethylchloroformate dropwise keeping the temperature at 2°C (36°F). This solution is stirred at 0°C (32°F) for 45 minutes.

25 A cooled solution of 7.8 g of 6-aminopenicillanic acid potassium salt (I), 4.2 ml of triethylamine and 9.6 ml of water is added all at once to the above mixed anhydride solution and stirred at room temperature until reaction is complete as per TLC (thin layer chromatography). The reaction mixture is washed with

30 dichloromethane then the aqueous layer is acidified to pH 2 with 1N HCl. The aqueous layer is extracted with dichloromethane and the combined organic extracts are washed with water, dried over sodium sulfate and concentrated in vacuo to yield Product (II).

35 Approximately 13.0 g of Product (II) is added to a stirred solution of mercury(II) acetate (12.8 g) in acetic acid (200 ml), at room temperature. Acetone is mixed with the resulting gel and

-106-

the insoluble material filtered off and washed with acetone and ether to give Product (III). An excess of diazomethane in ether is added to a stirred suspension of 11.9 g of the salt Product (III) in dimethyl sulfoxide (45 ml). After 2 hours the mixture is diluted with dichloromethane, filtered and washed with water. The organic layer is dried (sodium sulfate) and concentrated to give a mixture of products with the desired Product (IV) isolated by chromatography. This thiol (IV) (4.4 g) and mercury (II) acetate (1.08 g) in dimethyl sulfoxide (80 ml) are stirred for 18 hours. The mixture is then diluted with dichloromethane, filtered and washed with water. The organic layer is dried over sodium sulfate and evaporated to yield Product (V).

Approximately 2.95 g of Product (V) is dissolved in acetone (35 ml), and approximately 0.95 g of p-toluene sulfonic acid monohydrate is added. The mixture is stirred for 20 minutes at 18°C (64°F). The solvent is then evaporated to leave Product (VI), which is triturated. To a solution of 2.3 g of Product (VI) in dichloromethane (20 ml) is added 0.52 ml of phenoxyacetyl chloride with ice-bath cooling. This mixture is stirred and a solution of 0.55 ml of pyridine in dichloromethane (4 ml) is added during a period of 30 minutes. After stirring an additional 30 minutes, the mixture is concentrated, and the residue dissolved in dichloromethane, washed with dilute HCl, water, saturated sodium bicarbonate, and brine, and dried over sodium sulfate and evaporated to give Product (VII).

Product (VII) (approximately 0.91 g) is dissolved in 15 ml of acetone with 0.26 ml of acetic acid and cooled to 0°C (32°F). Approximately 0.25 g of potassium permanganate, dissolved in 10 ml of water, is added keeping the temperature at approximately 2°C (36°F). When the addition is complete, the mixture is warmed to room temperature and allowed to stir for 3 hours. The solid is then filtered, and washed with dichloromethane. The filtrate is diluted with water and the layers separated. The organic layer is washed with saturated sodium bicarbonate solution and water, dried and evaporated to give Product (VIII).

-107-

An anhydrous solution of approximately 0.46 g Product (VIII) in 4 ml of DMF is made, and approximately 0.95 g of DMF·SO₃ complex is added. This is allowed to stir 2 hours or until the reaction is complete as shown by TLC. The mixture is then diluted with 20 ml of dichloromethane and 20 ml of 0.5 N potassium hydrogen phosphate solution with stirring. The pH is adjusted to 6 with 1 N NaOH and 0.25 g of tetrabutylammonium hydrogen sulfate is added. The layers are separated and the organic layer is washed with water, dried and concentrated to yield Product (IX).

The product (IX) is taken up in approximately 10 ml of dichloromethane, 30 ml of water and 5 mg of bis(triphenylphosphine) palladium chloride. The mixture is treated with approximately 150 microliters of tributyl tin hydride while maintaining a temperature of approximately 21°C (70°F). After rapid stirring for approximately 5 minutes, the deprotected product is isolated by filtration. This is then taken up in water and methanol, filtered, and washed with water. The filtrate is concentrated to yield final Product (X) which is purified by trituration.

EXAMPLE 7

An antimicrobial composition for parenteral administration, according to this invention, is made comprising:

| | <u>Component</u> | <u>Amount</u> |
|----|--|-------------------|
| 25 | [5R][5 α ,6 α]-3-[[7-[(3-amino-1-pyrrolidiny)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-3-(1,8-naphthyridinyl)]carbonyloxy)methyl]- | |
| 30 | 6-(1(R)-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid ¹ | 100 mg/ml carrier |

-108-

Carrier:

sodium citrate buffer with (percent
by weight of carrier):

| | | |
|---|------------------------|-------|
| | lecithin | 0.48% |
| 5 | carboxymethylcellulose | 0.53 |
| | povidone | 0.50 |
| | methyl paraben | 0.11 |
| | propyl paraben | 0.011 |

1: a quinolonyl lactam ester, made according to Example 1

10

The above ingredients are mixed, forming a suspension. The above
Approximately 2.0 ml of the suspension is systemically administered, via intramuscular injection, to a human subject suffering from a lower respiratory tract infection, with Streptococcus pneumoniae present. This dosage is repeated twice daily, for approximately 14 days. After 4 days, symptoms of the disease subside, indicating that the pathogen has been substantially eradicated.

15

EXAMPLE 8

20

An enteric coated antimicrobial composition for oral administration, according to this invention, is made comprising the following core tablet:

25

30

35

| <u>Component</u> | <u>Amount (mg)</u> |
|--|--------------------|
| [5R][5 α ,6 α]-3-[[7-[(3-amino-1-pyrrolidinyl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-3-(1,8-naphthyridinyl)]carbonyloxy]methyl]-6-(1(R)-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid ¹ | 350.0 |
| starch | 30.0 |
| magnesium stearate | 5.0 |
| microcrystalline cellulose | 100.0 |
| colloidal silicon dioxide | 2.5 |
| povidone | 12.5 |

1: a quinolonyl lactam ester, made according to Example 1

-109-

The components are admixed into a bulk mixture. Compressed tablets are formed, using tableting methods known in the art. The tablets are coated with a suspension of methacrylate acid/methacrylate ester polymer in isopropanol/acetone. A human subject, having a urinary tract infection with Escherichia coli present, is orally administered two of the tablets, every 8 hours, for 14 days. Symptoms of the disease then subside, indicating substantial eradication of the pathogen.

10

15

20

25

30

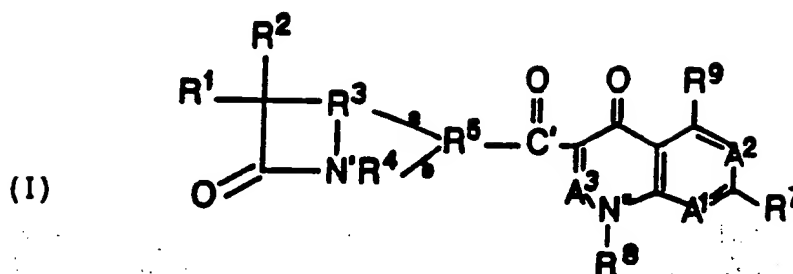
35

-110-

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of the general formula



wherein

- (A) R^1 is hydrogen, halogen, alkyl, alkenyl, heteroalkyl, a carbocyclic ring, a heterocyclic ring, $R^{10a}-O-$, $R^{10a}CH=N-$, $(R^{10})(R^{11})N-$, $R^{12}-C(=CHR^{15})-C(=O)NH-$, $R^{12}-C(=NO-R^{14})-C(=O)NH-$, or $R^{13}-(CH_2)_m-C(=O)NH-$, preferably alkyl, alkenyl, $R^{12}-C(=NO-R^{14})-C(=O)NH-$, or $R^{13}-(CH_2)_m-C(=O)NH-$; where
- (1) m is an integer from 0 to 9, preferably from 0 to 3;
 - (2) R^{10} and R^{11} are, independently, R^{10a} where R^{10a} is hydrogen, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring substituent; or R^{10} and R^{11} together comprise a heterocyclic ring including the nitrogen to which they are bonded;
 - (3) R^{12} is hydrogen, alkyl, alkenyl, heteroalkyl, heteroalkenyl, a carbocyclic ring, or a heterocyclic ring, preferably alkyl, a carbocyclic ring or a heterocyclic ring;
 - (4) R^{13} is R^{12} , $-Z^1$, or $-CH(Z^2)(R^{12})$;
 - (5) R^{14} is R^{12} , arylalkyl, heteroarylalkyl, $-C(R^{17})(R^{18})COOH$, $-C(=O)O-R^{12}$, or $-C(=O)NH-R^{12}$, preferably R^{12} or $-C(R^{17})(R^{18})COOH$; where R^{17} and R^{18} are, independently, R^{12} or together comprise a

-111-

carbocyclic ring or a heterocyclic ring including the carbon atom to which R¹⁷ and R¹⁸ are bonded;

- (6) R¹⁵ is R¹⁴, halogen, -Z¹, or -CH(Z²)(R¹²), preferably R¹⁴ or halogen;
- (7) Z¹ is -C(=O)OR¹⁶, -C(=O)R¹⁶, -N(R¹⁹)R¹⁶, -S(O)_pR²⁴, or -OR²⁴; and Z² is Z¹ or -OH, -SH, or -SO₃H;
 - (a) p is an integer from 0 to 2, preferably 0;
 - (b) R¹⁹ is hydrogen; alkyl; alkenyl; heteroalkyl; heteroalkenyl; a carbocyclic ring; a heterocyclic ring; -SO₃H; -C(=O)R²⁰; or, when R¹³ is -CH(Z²)(R¹²) and Z² is -N(R¹⁹)R¹⁶, R¹⁹ may comprise a moiety bonded to R¹⁶ to form a heterocyclic ring; and
 - (c) R²⁰ is R¹², NH(R¹²), N(R¹²)(R²¹), O(R²¹), or S(R²¹), preferably R¹², NH(R¹²), or N(R¹²)(R²¹); where R²¹ is alkyl, alkenyl, a carbocyclic ring, a heterocyclic ring, or when R²⁰ is N(R¹²)(R²¹) R²¹ may be a moiety bonded to R¹² to form a heterocyclic ring; and
- (8) R¹⁶ is R²⁴ or hydrogen, preferably hydrogen, alkyl, a carbocyclic ring or a heterocyclic ring; where R²⁴ is alkyl; alkenyl; arylalkyl; heteroalkyl; heteroalkenyl; heteroarylalkyl; a carbocyclic ring; a heterocyclic ring; or, when Z¹ is N(R¹⁹)R¹⁶ and R¹⁶ is R²⁴, R¹⁶ and R¹⁹ may together comprise a heterocyclic ring including the nitrogen atom to which R¹⁹ is bonded;
- (B) R² is hydrogen, halogen, alkoxy, or R²²C(=O)NH-, preferably hydrogen or alkoxy; where R²² is hydrogen or alkyl;
- (C) bond "a" is a single bond or is nil; and bond "b" is a single bond, a double bond, or is nil; except bond "a" and bond "b" are not both nil;
- (D) R³ is -C(R^{10a})-, or -CH₂-R²³-, preferably -C(R^{10a})-; where R²³ is -C(R^{10a}), -O-, or -N-, and R²³ is directly bonded to N' in Formula (I) to form a 5-membered ring; except, if bond "a" is nil, then R³ is
 - (1) -C(R^{10a})(Z³)-, where

-112-

(i) Z^3 is $-R^{16}$; $-OR^{25}$; $-S(O)_rR^{25}$, where r is an integer from 0 to 2, preferably 0; $-OC(=O)R^{25}$; or $-N(R^{25})R^{26}$;

(ii) R^{25} and R^{26} are, independently, alkyl, alkenyl, carbocyclic ring or heterocyclic ring substituents; or R^{25} and R^{26} together comprise a heterocyclic ring including the nitrogen atom to which R^{25} and R^{26} are bonded; or

(2) $-CH_2-R^{27}-$; where R^{27} is $-C(R^{10a})(R^{16})$, $-O-$, or $-NR^{10}$, and R^{27} is directly bonded to N in Formula (I) to form a 5-membered ring;

(E) (1) if bond "b" is a single bond, R^4 is $-CH(R^{28})-$; or, if bond "a" is nil; $-C(O)NHSO_2-$; or $-C^*(R^{28})-$; if R^5 contains a R^{32} moiety; where R^{28} is hydrogen or $COOH$, preferably $COOH$, and C^* is linked to R^{32} to form a 3-membered ring;

(2) if bond "b" is a double bond, R^4 is $-C(R^{28})=$; or

(3) if bond "b" is nil, R^4 is hydrogen, $-SO_3H$, $-PO(OR^{29})OH$, $-C(O)NHSO_2N(R^{29})(R^{30})$, $-OSO_3H$, $-CH(R^{30})COOH$, or $-OCH(R^{29})COOH$; preferably $-SO_3H$, or $-C(O)NHSO_2N(R^{29})(R^{30})$; where R^{29} is hydrogen, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring; and R^{30} is hydrogen, alkyl, alkenyl, or $-NHR^{10a}$; or, if R^4 is $-C(O)NHSO_2N(R^{29})(R^{30})$, R^{29} and R^{30} may together comprise a heterocyclic ring including the nitrogen to which R^{29} and R^{30} are bonded; and

(F) (1) if bond "a" or bond "b" is nil, then R^5 is Y ;

(2) if bond "a" and "b" are single bonds, R^5 is $-X^2-C''=C(R^{10a})-R^{31}-Y-$, or $-X^2-C''(R^{32})-R^{31}-Y-$; or

(3) if bond "a" is a single bond and bond "b" is a double bond, R^5 is $-C(R^{10a})(R^{33})-X^2-C''-R^{31}-Y-$; $-X^1-C(R^{10a})(R^{33})-C''-R^{31}-Y-$; or $-X^2-C''-R^{31}-Y-$; where

(a) X^1 is O or $C(R^{33})$, where R^{33} is hydrogen, alkyl or alkoxy;

(b) X^2 is O ; $S(O)_s$, where s is an integer from 0 to 2; or $C(R^{33})$;

-113-

- (c) R^{31} is nil, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring;
 - (d) R^{32} is hydrogen; alkyl; alkenyl; $-\text{COOH}$; or, if R^4 is $-\text{C}^*(R^{28})$, R^{32} may be linked to C^* to form a 3-membered carbocyclic ring;
 - (e) Y is O or $\text{Z}^4\text{-R}^{34}\text{-O}$, where
 - (1) Z^4 is $-\text{O}-$; $-\text{S}(\text{O})_t-$, where t is an integer of 0 to 2; or $-\text{NR}^{10a}-$; and
 - (2) R^{34} is alkyl, alkenyl, heteroalkyl, heteroalkenyl, a carbocyclic ring, or a heterocyclic ring; and
 - (3) Y is directly bonded to C'
 - (f) C'' is bonded to R^4 to form a 5- or 6-membered ring;
- (G)
- (1) A^1 is N or $\text{C}(\text{R}^{40})$; where R^{40} is hydrogen, hydroxy, alkoxy, nitro, cyano, halogen, alkyl, or $\text{N}(\text{R}^{10})(\text{R}^{11})$, preferably hydrogen or halogen;
 - (2) A^2 is N or $\text{C}(\text{R}^6)$, preferably $\text{C}(\text{R}^6)$; where R^6 is hydrogen or halogen;
 - (3) A^3 is N or $\text{C}(\text{R}^{41})$, preferably $\text{C}(\text{R}^{41})$; where R^{41} is hydrogen;
 - (4) R^8 is hydrogen, alkyl, a carbocyclic ring, a heterocyclic ring, alkoxy, hydroxy, alkenyl, arylalkyl, or $\text{N}(\text{R}^{10})(\text{R}^{11})$, preferably alkyl or a carbocyclic ring;
 - (5) R^7 is hydrogen, halogen, alkyl, a carbocyclic ring, or a heterocyclic ring, preferably a heterocyclic ring; and
 - (7) R^9 is hydrogen, halogen, nitro, or $\text{N}(\text{R}^{10})(\text{R}^{11})$, preferably hydrogen;
- (H) except that
- (1) when A^1 is $\text{C}(\text{R}^{40})$, R^8 and R^{40} may together comprise a heterocyclic ring including N'' and A^1 ;
 - (2) when A^2 is $\text{C}(\text{R}^6)$, R^6 and R^7 may together comprise $-\text{O}-(\text{CH}_2)_n\text{-O}-$, where n is an integer from 1 to 4; and

-114-

(3) when A³ is C(R⁴¹), R⁸ and R⁴¹ may together comprise a heterocyclic ring including N" and the adjacent carbon to which R⁴¹ is bonded; and pharmaceutically-acceptable salts and biohydrolyzable esters thereof, and hydrates thereof.

2. A compound, according to Claim 1, containing a lactam-containing moiety selected from the group consisting of: oxacephems, carbacephems, isocephems, iso-oxacephems, penems, carbapenems, clavams, penicillins, clavams, 2,3-methylene-penems, 2,3-methylene-carbapenems, and pyrazolidinones; preferably isocephems, oxacephems, carbacephems, penicillins, and carbapenems.

3. A compound, according to Claim 2, wherein said lactam-containing moiety is selected from the group consisting of penems and carbapenems.

4. A compound, according to Claim 1, containing a lactam-containing moiety selected from the group consisting of: monobactams, monophosphams, monocarbams, monosulfactams, nocardicins, lactivicin analogs, and gamma-lactams; preferably a monobactam.

5. A compound, according to Claim 2, wherein R² is hydrogen or alkoxy and R³ is -C(R^{10a})-.

6. A compound, according to Claim 4, wherein R² is hydrogen or alkoxy and R³ is -C(R^{10a})-.

7. A compound according to Claim 1, wherein: A¹ is nitrogen or C(R⁴⁰), preferably nitrogen; A² is C(R⁶); and A³ is (R⁴¹).

8. A compound according to Claim 7, containing a 6-fluoroquinolone moiety, a 8-halo-6-fluoroquinolone moiety, a pyridobenzoxazine moiety, a pyridobenthiazine moiety, a isothiazoloquinolinedione, or isoxazoloquinolinedione moiety.

9. A compound, according to Claim 7, wherein: R⁸ is alkyl, aryl, cycloalkyl or alkylamino, preferably ethyl, 2-fluoroethyl, 2-hydroxyethyl, t-butyl, 4-fluorophenyl, 2,4-difluorophenyl, methylamino or cyclopropyl; and R⁴⁰ is hydrogen, chlorine or fluorine.

10. A compound, according to Claim 8, wherein R⁷ is a nitrogen-containing heterocyclic ring, preferably piperazine, 3-methylpiperazine, 3-aminopyrrolidine, 3-aminomethylpyrrolidine, N,N-dimethylaminomethylpyrrolidine, N-methylaminomethylpyrrolidine, N-ethylaminomethylpyrrolidine, pyridine, N-methylpiperazine, or 3,5-dimethylpiperazine.

11. A compound, according to Claim 9, wherein R⁸ is cyclopropyl, R² is fluorine, and R⁷ is piperazine.

12. A composition for treating or preventing an infectious disorder in a human or other animal subject, comprising:

- (1) a safe and effective amount of a compound of any of Claims 1 through 10; and
- (2) a pharmaceutically-acceptable carrier.

13. A composition for treating or preventing an infectious disorder in a human or other animal subject, according to Claim 11, wherein said composition is suitable for parenteral administration.

14. A composition for treating or preventing an infectious disorder in a human or other animal subject, according to Claim 11, wherein said composition is suitable for oral administration.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US89/04803

| I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC(5): C07D 499/00; A61K 31/425 U.S.Cl.: 514/192; 514/195; 540/310 | | | | | | | | | | | | | | |
|--|--|-------------------------------------|--|--|-------------------------------------|---|--|--|-----|--|--|-----|---|--|
| II. FIELDS SEARCHED <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black; margin: 5px 0;">Minimum Documentation Searched ⁷</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 30%; border-bottom: 1px solid black;">Classification System</th> <th style="border-bottom: 1px solid black;">Classification Symbols</th> </tr> <tr> <td style="vertical-align: top; padding: 5px;">U.S.</td> <td style="vertical-align: top; padding: 5px;">514/192; 514/194; 514/195 540/310; 540/350</td> </tr> </table> <div style="border-top: 1px solid black; padding-top: 5px; margin-top: 5px;"> Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸ </div> | | | Classification System | Classification Symbols | U.S. | 514/192; 514/194; 514/195 540/310; 540/350 | | | | | | | | |
| Classification System | Classification Symbols | | | | | | | | | | | | | |
| U.S. | 514/192; 514/194; 514/195 540/310; 540/350 | | | | | | | | | | | | | |
| CAS ON LINE (COMPUTER SEARCH) | | | | | | | | | | | | | | |
| III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹ <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%; border-bottom: 1px solid black;">Category ⁴</th> <th style="width: 70%; border-bottom: 1px solid black;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 20%; border-bottom: 1px solid black;">Relevant to Claim No. ¹³</th> </tr> <tr> <td style="vertical-align: top; padding: 5px;">A,P</td> <td style="vertical-align: top; padding: 5px;">US, A, 4,794,109 (LANG) published 27 December 1988, see entire document.</td> <td style="vertical-align: top; padding: 5px;"></td> </tr> <tr> <td style="vertical-align: top; padding: 5px;">A,P</td> <td style="vertical-align: top; padding: 5px;">US, A, 4,849,419 (BARKER ET AL) published 29 August 1989, see entire document.</td> <td style="vertical-align: top; padding: 5px;"></td> </tr> <tr> <td style="vertical-align: top; padding: 5px;">A,P</td> <td style="vertical-align: top; padding: 5px;">US, A, 4,861,768 (TORII ET AL) published 19 July 1989, see entire document.</td> <td style="vertical-align: top; padding: 5px;"></td> </tr> </table> | | | Category ⁴ | Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹² | Relevant to Claim No. ¹³ | A,P | US, A, 4,794,109 (LANG) published 27 December 1988, see entire document. | | A,P | US, A, 4,849,419 (BARKER ET AL) published 29 August 1989, see entire document. | | A,P | US, A, 4,861,768 (TORII ET AL) published 19 July 1989, see entire document. | |
| Category ⁴ | Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹² | Relevant to Claim No. ¹³ | | | | | | | | | | | | |
| A,P | US, A, 4,794,109 (LANG) published 27 December 1988, see entire document. | | | | | | | | | | | | | |
| A,P | US, A, 4,849,419 (BARKER ET AL) published 29 August 1989, see entire document. | | | | | | | | | | | | | |
| A,P | US, A, 4,861,768 (TORII ET AL) published 19 July 1989, see entire document. | | | | | | | | | | | | | |
| <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div> | | | | | | | | | | | | | | |
| IV. CERTIFICATION <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; vertical-align: top; padding: 5px;"> Date of the Actual Completion of the International Search 26 JANUARY 1990 International Searching Authority </td> <td style="width: 50%; vertical-align: top; padding: 5px;"> Date of Mailing of this International Search Report <div style="text-align: center; font-size: 1.2em; font-weight: bold;">31 JAN 1990</div> Signature of Authorized Officer <div style="text-align: center;"> NICHOLAS S. RIZZO </div> </td> </tr> </table> | | | Date of the Actual Completion of the International Search 26 JANUARY 1990 International Searching Authority | Date of Mailing of this International Search Report <div style="text-align: center; font-size: 1.2em; font-weight: bold;">31 JAN 1990</div> Signature of Authorized Officer <div style="text-align: center;"> NICHOLAS S. RIZZO </div> | | | | | | | | | | |
| Date of the Actual Completion of the International Search 26 JANUARY 1990 International Searching Authority | Date of Mailing of this International Search Report <div style="text-align: center; font-size: 1.2em; font-weight: bold;">31 JAN 1990</div> Signature of Authorized Officer <div style="text-align: center;"> NICHOLAS S. RIZZO </div> | | | | | | | | | | | | | |

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers _____, because they relate to subject matter¹² not required to be searched by this Authority, namely:

2. ☐ Claim numbers _____, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out¹³, specifically:

3. ☐ Claim numbers _____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

This International Searching Authority found multiple inventions in this international application as follows:

See Attachment sheet 1.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers: **claims 1-13 (in part)**

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

PCT/US89/04803
Attachment sheet 1

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I. Penems. Claims 1-13 (in part)

Group II. Cephalosporins. Claims 1-13 (in part)

Group III. Monocyclic Beta-lactams. Claims 1-13 (in part)

Group IV. Oxacephems. Claims 1-13 (in part)

Group V. Carbacephems. Claims 1-13 (in part)

Group VI. Carbapenems. Claims 1-13 (in part)

The inventions listed as Groups I, II, III, IV, V, VI do not meet the requirements for Unity of Invention for the following reasons:

Each of the groups lack "unity of invention" because of structural dissimilarity, each requires separate search in the literature and in the patents and each is separately classified. Each requires separate and distinct considerations for patentability and each will support separate patents.

During a telephonic requirement for election, on January 3, 1989 applicant's representative, Mr. Witte, elected the invention of Group I for examination. No additional examination fees were authorized and only one invention was elected.